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METASTATIC TUMOURS IN THE THYREOID GLAND *

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I. INTRODUCTION

Malignant neoplasms of many kinds are distributed embolically in the arterial blood stream, and establish secondary tumours in various tissues. One of the most neglected problems of oncology is that of the preferential tissue affinities of the different types of malignant cell. Certain tissues and organs, for example the liver, are very frequent sites of metastases from neoplasms of very diverse kinds; while other tissues and organs, such as the skeletal muscles or the intestinal tract, are rarely the seat of malignant metastasis. Moreover, various tumours display decided predilections in the distribution of their metastases, notorious examples of this being the frequency of secondary growths in bones in cases of renal or of thyreoid carcinomata. For the many vagaries of metastatic distribution observed in individual cases of malignant disease, no generally satisfactory explanations have been advanced. Various mechanical theories have been suggested, as for example that the movement of certain tissues inhibits the effective embolic lodgement of malignant elements; and the permeability of the capillaries of various tissues for minute solid particles has been much discussed. Other workers, however, have held that chemical rather than mechanical and circulatory factors play the principal rôle in determining the sites of development of metastatic growths. Thus Paget (1889)[1] speaks of certain tissues as being "congenial soil" for malignant growth, and views favourably the conception of Fuchs that

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certain organs may be "predisposed" for the growth of malignant emboli; and Mallory (1914)[2] in referring to this problem says "Conditions of a chemical nature probably play an important part." Ewing (1928)[3] expresses the opposite view in the statement that "there is as yet no evidence that any one parenchymatous organ is more adapted than others to the growth of embolic tumor-cells."

I have been struck by the relative immunity from malignant metastases displayed by certain richly arterialised organs. In cases of systemic haematogenous dissemination of malignant tumours, the embolic influx into the various tissues of the body must be proportional to their respective arterial blood supplies, yet such richly vascular organs as the intestine, the spleen and the thyreoid gland, are amongst the least frequent sites of development of secondary growths. Most noteworthy in this respect is the thyreoid gland, which, next to the adrenal gland, is the most richly arterialised tissue in the body. The adrenal gland receives approximately 650 cc. of arterial blood per 100 grams of tissue per minute, and thrice this amount during a rise of blood pressure produced by adrenalin (Neuman, 1912).[4] The corresponding figure for the thyreoid gland is only slightly less, namely 560 cc. per 100 grams per minute (Burton-Opitz, 1910).[5] With these high figures may be contrasted, for example, the relatively scanty arterial supply of the liver which receives only 26 cc. of arterial blood per 100 grams per minute (Burton-Opitz), or, according to Barcroft and Shore (1912),[6] 12 cc. for the resting liver and 23 cc. for the active liver subsequent to the digestion and absorption of food. Taking the total weights of the liver and thyreoid gland to be 1500 and 25 grams respectively, it will be seen that the thyreoid actually receives approximately one-half the volume of arterial blood received by the entire liver. Yet, while the liver is very frequently the seat of metastases from tumours of diverse kinds distributed in the systemic blood stream, metastatic growths in the thyreoid gland are unusual. The striking disparity between the arterial vascularity and the incidence of metastatic neoplasms in thyreoid tissue decided me to make a study of secondary tumours in this organ, with a view to determining, if possible, whether circulatory or chemical factors appeared to afford the better explanation of that disparity.

II. Review of the Literature

The following résumé of recorded cases which exhibited metastatic tumours in the thyreoid makes no claim to completeness. A reasonably careful search has been made of available pathological literature, but doubtless a number of isolated case reports in which thyreoid metastases are recorded have escaped discovery. However, the material reviewed is adequate for the purposes of this paper, and the writer hopes that no important references on the subject have been omitted. A description is given first of those cases in which metastatic growths in the thyreoid exhibited some noteworthy peculiarity, such as a special relationship to other pathological conditions of the gland. Then follows briefer reference to cases in which no details concerning the condition of the organ are recorded, or in which no striking peculiarity was observed.

Virchow in his book on tumours,[7] stated that malignant goitre might be either primary or secondary, that the latter might be either by direct extension from neighbouring growths or by metastasis from remote parts, and that cancerous or sarcomatous metastases might lodge in a thyreoid gland already goitrous. Virchow exemplified such metastatic growths by two cases. The first case was that of a goitrous cretin, aged 53 years, who had had a testicular tumour removed eight years previously. At autopsy the old nodular goitrous thyreoid contained a prominent tumour mass consisting of cells with large nuclei, and similar tumours were present in the lungs and sternum. Despite the long intervening period, Virchow regarded these several growths as metastases from the testicular tumour, and not as primary carcinoma of the thyreoid. Virchow's second case was a female, aged 65 years, with a primary growth of the posterior pharyngeal wall. The thyreoid gland, which exhibited diffuse colloid goitre, was the seat of two prominent metastatic tumours. Other secondary growths were present in the pancreas and kidney. In the same work, speaking of malignant melanotic tumours, Virchow also remarked of the less frequent sites of metastases that "the thyreoid gland appears to be involved more frequently than the spleen."

Kaufmann in his Lehrbuch (Reimann's translation 1929, p. 537)[8] remarks the infrequency of metastatic neoplasms in the thyreoid gland, and states his experience that melanotic growths are the most

frequently encountered, an opinion confirming that of Virchow to which reference has been made above. Kaufmann also mentions the case of a woman, aged 59 years, in whom an ovarian carcinoma produced minute metastases in an adenoma of the thyreoid and in no other part of the gland.

Naegeli (1912)[9] records the case of an elderly female in whom an adenocarcinoma of the rectum produced metastases in thyreoid adenomata. The thyreoid had been the seat of long-standing irregular enlargement, and the cancerous deposits were most prominent in the degenerated adenomatous areas. A small probable metastasis in one lung was not examined microscopically.

Kettle (1912)[10] mentions a case in which he observed in an adenoma of the thyreoid, a metastasis from a squamous carcinoma of the uterus.

Rost (1912)[11] describes the case of a man, aged 48 years, with "hypernephroma" metastases in the lungs, clavicle, thyreoid and many lymph glands. The thyreoid was much enlarged by long-standing goitrous changes, and contained also an area of secondary growth. The malignant elements were separated from the surrounding thyreoid tissue by a wide zone of connective tissue, and from Rost's description it is apparent that the metastasis had become established in a fibrosed area of the goitrous gland.

Müller (1912)[12] describes a male patient, aged 64 years, who died with haemangiomatous growths in the gums, pleura, lungs, bowel, bones and thyreoid gland. This organ was much enlarged: the right lobe was extensively calcified; the left lobe contained many adenomata, and in one of these, 2.5 cm. in diameter, there was an angiomatous nodule 8 mm. in diameter. While inclining to the view that the condition was a "system disease" involving the vessels of the various organs, Müller admits the possibility of metastasis from one of the tumours as a primary focus. Microscopically the growths presented the structure of cavernous angioma, with however, proliferation of the endothelial cells which in places were desquamating into the vascular spaces.

Most pathologists accept the neoplastic character of chloroma which therefore may be included legitimately in the present paper.

Sauer (1914)[13] describes a case of this disease in a male, aged 36 years, exhibiting in addition to other lesions, chloroma nodules in the thyreoid, spleen, kidneys and prostate. The thyreoid gland was

decidedly enlarged, and contained a number of well defined greenish nodules in both lobes. These proved to be thyreoid adenomata infiltrated by chloroma cells which extended thence into the adjacent, more normal thyreoid tissue. Sauer could discover only one other previously recorded case of chloromatous deposits in the thyreoid gland, described by *Pribram* (1909)[14] in a male, aged 22 years.

Herxheimer (1925)[15] describes diffuse myeloblastic infiltration of the thyreoid in a case of leukaemia.

Reinhart (1917)[16] records the case of a female patient, aged 38 years, who suffered from carcinoma of the left lung with metastases in the right lung, pleura, kidneys, adrenals, liver, thyreoid, lumbar spine, and thoracic and retroperitoneal lymph glands. In the right lung and in the bronchial glands, chronic tuberculosis coexisted with the malignant disease. The thyreoid, only slightly enlarged, contained several metastatic nodules of growth, and was also the seat of tuberculous disease with fibrosis, lymphocyte accumulation, and numbers of tubercles. Reinhart remarks on the unusual combination of cancerous metastasis and tuberculous disease of the thyreoid which is an infrequent site of either of these conditions, and suggests the possibility of a causal relationship of the *locus minoris resistentiae* kind.

Prym (1924)[17] records a case of chorionepithelioma in a woman, aged 44 years. Metastases were present in the lungs, brain, liver, bowel mucous membrane, both kidneys and thyreoid gland. This last organ was the seat of multiple adenomata, and the metastatic deposit was located within one of the adenomatous areas.

In the above cases the striking relationship of the metastatic growths in the thyreoid gland to other abnormalities necessitated special comment. In many other cases no such noteworthy associations are recorded, or, more often, no details whatever are available concerning the condition of the organ. It is not necessary, therefore, to describe these cases individually, and the abbreviated information given in the following list will suffice.

Foerster (1858).[18] Carcinoma of cervix uteri.
Rosenblatt (1867).[19] Carcinoma of liver.
Blau (1870).[20] Carcinoma of corpus uteri.
Beck (1884).[21] Carcinoma of lung. Male, 65 years.
Siegel (1887).[22] Carcinoma of lung. Female, 68 years.
Ehrich (1891).[23] Carcinoma of lung. Female, 52 years.
Kantorowicz (1893).[24] Carcinoma of breast. Female, 51 years.

Kaufmann (1902).[25]
(1) Malignant rhabdomyoma of prostate. Male, 26 years.
(2) Carcinoma of prostate. Male, 43 years.
Kaufmann (Lehrbuch, Reimann's translation, 1929).[8]
(1) Carcinoma of pharynx. Male, 62 years. (p. 824.)
(2) Adenocarcinoma of uterus. Female, 73 years. (p. 1681.)
Hirschfeld (1906).[26] Sarcoma of ala of ilium. Male, 36 years.
Grimm (1907).[27] Carcinoma of breast.
Offergeld (1909).[28] This author in a study of metastases from uterine cancer found records of seven cases with thyreoid metastases. The original account is not immediately available to the present writer.
Davidsohn (1911).[29] Malignant melanoma of adrenal. Male, 58 years.
Chalier and Bonnet (1912).[30] Malignant melanoma of rectum. Male, 48 years.
Kettle (1912).[10] Squamous carcinoma of breast. Female, 69 years.
Mori (1913).[31]
(1) Malignant melanoma of eye. Male, 43 years.
(2) Carcinoma of breast. Female, 42 years.
(3) Carcinoma of breast.
Schöppler (1917).[32] Carcinoma of lung. Adult male.
Handley (1922).[33] Malignant melanoma of skin. Female, 34 years.
Jeannée (1925).[34]
(1) Carcinoma of bronchus. Male, 39 years.
(2) Malignant melanoma of skin. Female, 42 years.
(3) Carcinoma of bronchus. Male, 54 years.
Chajutin (1926).[35] Carcinoma of liver. Male, 60 years.
Derischanoff (1926).[36] Carcinoma of breast. Female, 58 years.
di Biasi (1926).[37]
(1) Squamous carcinoma of breast. Female, 47 years.
(2) Carcinoma of breast. Female, 48 years.
(3) Naevus carcinoma of skin. Male, 52 years.
(4) Carcinoma of breast. Female, 69 years.
(5) Malignant melanoma of adrenal region. Male, 83 years.
(6) Carcinoma of breast. Female, 73 years.
(7) Carcinoma of breast. Female, 60 years.
(8) Carcinoma of lung. Male, 52 years.
In two other cases described by di Biasi, metastases recorded in the thyreoid were queried, these two cases therefore are excluded.
White and Brunton (1927).[38] Brief reference is made to two cases in which it is stated that thyreoid metastases were present, but information given is inadequate to justify inclusion.
Brandt (1927).[39] Carcinoma of kidney. Female, 75 years.
Girdwood (1929).[40] Malignant melanoma of skin. Female, 42 years.

If we regard Hodgkin's "granuloma" as neoplastic in nature, involvement of the thyreoid in that disease also falls in the scope of this paper. Osler (1885)[41] mentions two cases of thyreoid enlargement due to deposits of "Hodgkin's tissue," but gives no details. Beitzke (1909)[42] described a case of Hodgkin's disease in a woman, aged 65 years, in which the lymph glands of the upper parts of the

body were involved, and tumour-like masses were present in the bone marrow, skull periosteum, liver and thyreoid gland.

Finally, mention must be made of three cases referred to by Ewing (1928, p. 961),[3] namely Pick's and Ehrhardt's cases of osteosarcoma and Fraenkel's case of melanosarcoma. As the original reports are not immediately accessible, and as there appears to be doubt as to whether the tumours in the thyreoid were primary or secondary, I have excluded these cases from further consideration in this paper.

III. Personal Observations

The following examples of metastatic tumours in the thyreoid gland have been observed by the writer in personally conducted autopsies. The descriptions are abbreviated, but all essential details are included.

Case I. *Clinical History:* Male, 47. In 1923, left eyeball excised for pigmented intra-ocular tumour. Good health thereafter for over four years. July 1927, recurrence of tumour in orbital cavity, and clinical enlargement of liver. Death in February 1928.

Autopsy Findings: Recurrent melanotic tumour of orbit. Numerous partly pigmented, partly colourless metastases in the myocardium, endocardium, right lung, liver (280 ounces), kidneys, both adrenals, retroperitoneal tissues and thyreoid gland. The latter, otherwise normal, contained a solitary pigmented metastasis 1.5 cm. in diameter in the left lobe.

Histological Findings: Tumour cells, both polyhedral and fusiform, arranged both diffusely and in discrete clumps in relatively scanty stroma. Pigment formation varies in degree in different areas, in places absent, in places massive, both intra- and extracellular in situation.

Case II. *Clinical History:* Female, 54. January 1927, "indigestion" appeared. June 1927, radical excision of rectum after preliminary colostomy. Good health thereafter for nearly two years. April 1929, pain in right leg and some difficulty with micturition; vaginal examination revealed large hard mass occupying right side of pelvic cavity. Death in September 1929.

Autopsy Findings: Large firm cancerous mass in pelvic cavity, adherent to sacrum and right pelvic wall, and infiltrating perineum and lower part of uterus. A moderate number of small scattered

metastases in the liver, spleen, kidneys, adrenals, pancreas, dura mater, several ribs and thyreoid gland. The last named organ was small and of normal external appearance, but on section a metastasis 1 cm. in diameter was found in the upper pole of the right lobe (Fig. 1), and two smaller separate nodules 3 mm. in diameter near the isthmus. The thyreoid tissue throughout was pale and tough and exhibited irregular strands of fibrous tissue. Subsequent microscopic study revealed extensive fibrosis, parenchymatous atrophy, and plentiful accumulations of lymphocytes.

Histological Findings: Anaplastic polyhedral and signet-celled carcinoma, in parts exhibiting loose alveolar formation, in parts diffuse; scanty suggestions of adenomatous grouping; mitoses plentiful; stroma scanty; much degenerative change (Fig. 2).

Case III. *Clinical History:* Female, 61. January 1929, patient noticed a small lump in left breast. June 1929, paresis of left limbs appeared, with spasticity and extensor plantar reflex on left side. Thereafter, rapid emaciation and asthenia, mild convulsive spasms of left arm, and aphasia. Death in August 1929.

Autopsy Findings: Non-ulcerating mass 5 cm. in diameter in left breast, adherent to skin and invading pectoral muscles; tissue partly dense and hard, partly soft and mucoid. Apical axillary and supraclavicular glands involved with extension to upper two ribs and intercostal spaces. Numerous small nodules of growth beneath visceral and parietal pleura on both sides; a few metastases in lung substance. Metastases also present in liver, left kidney, both adrenals, dura mater, cerebrum and the thyreoid gland. This organ was somewhat enlarged and exhibited irregular colloid retention and many small adenomata and cysts. It contained a solitary metastasis 1 cm. in diameter in the right lobe near the isthmus (Fig. 3).

Histological Findings: Primary tumour an adenocarcinoma with extensive areas of mucoid change. Metastases similar, but less prominently adenomatous and more often carcinoma simplex in type (Figs. 4 and 5).

Case IV. *Clinical History:* Female, 70. A firm mass the size of a walnut in left breast for 30 years. Early in 1928 this began to enlarge. December 1929, rapid growth of mass with cough and dyspnoea. By January 1930, mass was a firm hemispherical tumour 10 cm. in diameter projecting anteriorly, adherent to skin but not to muscles or chest wall. Death in February 1930.

Autopsy Findings: Mammary tumour restricted to fat and not involving pectoral muscles; axillary glands not enlarged. Numerous large metastases in both lungs and in parietal pleurae and mediastinal glands. A few small nodules in the liver. Thyreoid, of normal size, contained several adenomata up to 1 cm. in diameter; and the left lobe presented two tiny firm white nodules which proved microscopically to be metastases. These were not situated in adenomatous tissue.

Histological Findings: Anaplastic spindle and polyhedral-celled carcinoma, largely diffuse but partly alveolar in arrangement; numerous mitoses; scanty stroma.

CASE V. Female, 58. (Reported in detail elsewhere.)[43] Anaplastic carcinoma of breast; thyreoid almost totally replaced by metastatic growth; clinical symptoms of myxoedema.

CASE VI. Female, 41. (Reported in detail elsewhere.)[44] Malignant sacral chordoma with widespread metastases. The thyreoid gland was enlarged to double its normal size and was the seat of prominent fibrosis and many adenomata. Several chordoma metastases were present, the largest 8 mm. in diameter (Fig. 6). Several of these lay within adenomatous areas. Microscopically the thyreoid tissue exhibited extensive fibrosis, parenchymatous atrophy and lymphocytic infiltration (Fig. 7).

CASE VII. *Clinical History:* Female, 53. September 1929, postprandial epigastric pain and loss of weight. December, laparotomy revealed inoperable gastric cancer. Death in March 1930.

Autopsy Findings: Extensive gizzard carcinoma of the stomach with metastases in the coeliac and upper lumbar lymph nodes, the liver, peritoneum, ribs, sternum, skull and thyreoid. Microscopic tumour emboli were found also in the lungs. The thyreoid gland was small, pale and tough, and contained a single metastatic nodule 6 mm. in diameter.

Histological Findings: A disorderly adenocarcinoma. The metastasis in the thyreoid (Fig. 8) consisted of irregular acini of columnar-celled carcinoma set in an abundant, partly hyalinised fibrous stroma, which extended into the adjacent thyreoid tissue where cystic and calcareous changes were also present.

CASE VIII. *Clinical History:* Male, 73. Intermittent haematuria began in 1925. Pain in right loin and sacro-iliac region began in 1927. A swelling appeared in the latter situation in 1928. This

steadily enlarged. Haematuria continued; fibrinuria also present, the urine sometimes being very viscid and almost gelatinous. Skiagrams revealed erosion of the right ilium. Died July 1930.

Autopsy Findings: Large tumour of left kidney (28 ounces) with gross invasion of renal vein and projection of tumour into inferior vena cava. Metastases in lungs, liver, pancreas, thyreoid gland, ribs and ilium. The caudal pole of the right lobe of the thyreoid contained an irregular haemorrhagic metastasis 2 cm. in diameter with several neighbouring but connected satellite nodules (Fig. 9).

Histological Findings: Typical clear-celled papillary carcinoma of the kidney (Fig. 10). The thyreoid tissue exhibited some general fibrosis, vascular degeneration and pigmentation, but these changes were not excessive for the patient's age.

CASE IX. *Clinical History:* Female, 56. January 1929, pain and lump noticed in left breast; radical amputation in April; carcinoma simplex with axillary glands involved. September 1929, recurrence in right breast; amputation; carcinoma simplex; subsequent local recurrence and signs of intrathoracic extension. Died October 1930.

Autopsy Findings: Extensive nodular infiltration of both pectoral regions, with invasion of intercostal spaces and extensive involvement of pleurae and thoracic lymph glands. Metastases in liver, adrenals, peritoneum, abdominal and cervical lymph nodes, dura and thyreoid. The thyreoid was small, tough and poorly vesicular, and contained eight to ten metastatic nodules up to 5 mm. in diameter, as well as several diffuse areas of infiltration.

Histological Findings: Small spheroidal-celled carcinoma simplex. The thyreoid metastases occurred both as localised nodules and as diffuse infiltrations (Fig. 11). The thyreoid tissue itself was the seat of advanced fibrosis, parenchymatous atrophy and irregular adenoma formation with distorted irregular vesicles poor in colloid. Several of the metastatic nodules lay in the centres of adenomatous areas.

CASE X. *Clinical History:* Male, 54. April 1930, noticed small nodule in right ear near meatus. A month later mass appeared in neck just below ear. By June the ear nodule had become an ulcer 1.5 cm. in diameter on the inner aspect of the pinna, and there was a hard mass of glands in the upper cervical region. Diathermy of the ulcer given and radium needles buried in glands. Temporary improvement, but died in October 1930.

Autopsy Findings: Nodular recurrence in caudal wall of meatus, and large infiltrating mass in neck. Internal jugular vein obliterated and invaded and contained friable tumour thrombus. Massive metastases in lungs and thoracic lymph glands. A few small metastases in left kidney, right rectus abdominis muscle, mesentery, inguinal glands of both sides, and thyreoid. This last organ, otherwise substantially normal, contained two small white nodules each 4 mm. in diameter.

Histological Findings: Highly anaplastic non-cornifying epidermoid carcinoma with many mitoses, many giant tumour cells and frequent diffuse arrangement. The white nodules in the thyreoid proved to be small spherical adenomatous areas containing infiltrating metastatic tumour deposits (Fig. 12).

IV. Discussion and Deductions

The frequency of metastatic growths in the thyreoid gland

The numerical incidence of secondary tumours in any given organ is difficult to assess with accuracy, and this difficulty is greater in the case of certain organs which unfortunately are not always examined at autopsy with the same thoroughness as the major viscera. In many collected statistics which contain valuable figures concerning the incidence of metastatic growths in the lungs, liver, spleen and other principal organs, one feels less confident of the information relating to such viscera as the testis, the pituitary body or the thyreoid. Probably the German and other continental pathologists are the least fallible in this respect, and the following figures given by Müller (1892)[45] may be cited. In 521 autopsy cases of carcinoma, in which metastases were present in 47.2 per cent., the thyreoid gland was involved in 1.5 per cent. In 102 cases of sarcoma, 63.7 per cent. of which exhibited metastases, the thyreoid was involved in 3.1 per cent. Kitain (1922),[46] in a statistical study of 452 autopsies on cases of cancer, found the thyreoid gland the seat of metastases in 14 (*i. e.*, 3.1 per cent.), the sites of primary growth being breast 8, skin 1, larynx 1, pancreas 1, pharynx 1, thymus 1, lung 1.

My own experience suggests that the thyreoid is more frequently the seat of metastatic deposits than is generally recognised. Of my

ten cases, nine occurred in a series of 170 consecutive autopsies on unselected malignant cases of all kinds, the incidence of metastases in the thyreoid thus being 5.2 per cent. Admittedly no statistical deductions can be made from so small a series of cases; nevertheless I attribute this relatively high incidence of thyreoid deposits at least in part to the fact that the gland in each case was dissected out and thoroughly sectioned, a procedure not always adopted in routine autopsy work. Had this not been done, the metastases present in Cases II, IV, VII, IX and X could readily have eluded discovery. From personal experience, I am satisfied that mere bilateral section of the thyreoid in situ, a procedure frequently adopted, is an inadequate examination of the organ.

INFLUENCE OF TUMOUR-TYPE AND ORIGIN ON FREQUENCY OF THYREOID METASTASES

Little reliable information can be obtained from the literature regarding the relative incidences of thyreoid metastasis from various

	Cases
Carcinoma of breast	15
Malignant melanoma	9
Carcinoma of bronchi and lungs	8
Carcinoma of uterus	4
Carcinoma of kidney	3
Chloroma	2
Carcinoma of liver	2
Carcinoma of rectum	2
Carcinoma of pharynx	2
Carcinoma of stomach	1
Carcinoma of testis	1
Carcinoma of ovary	1
Carcinoma of prostate	1
Malignant rhabdomyoma of prostate	1
Carcinoma of skin of ear	1
Haemangio-endothelioma	1
Malignant sacral chordoma	1
Choriocarcinoma	1
Sarcoma of bone	1
Total	57

individual tumour groups. Kaufmann's impression that the incidence is relatively high in the case of melanotic growths receives statistical confirmation from the figures given by Eiselt (1861),[47] who, in 50 autopsies on such cases, found an incidence of 12 per

cent. This figure much exceeds the estimates cited above for malignant tumours in general.

Further information on the relationship between the type and origin of the primary neoplasm and the frequency of thyreoid metastases may be obtained by a tabulation of the origins of the 57 tumours reviewed in this paper.

The high place occupied by carcinoma of the breast is doubtless due to the great frequency of that disease. Yet it is noteworthy that an almost equally frequent neoplasm, gastric carcinoma, is poorly represented. Melanoma and lung carcinoma, both relatively uncommon tumours, take second and third places on the list. Lung cancer, which is recognised as possessing an unusual tendency to metastasise to the brain and adrenal glands (Dosquet, 1921),[48] evidently exhibits also a similar predilection for the thyreoid. The position occupied by melanoma in the table confirms the relatively high incidence of thyreoid metastases in this disease remarked by Kaufmann and by Eiselt.

THE RELATION OF METASTASES TO PREËXISTING ABNORMALITIES OF THE THYREOID

Frequently, records of secondary growths in the thyreoid give no detail regarding the condition of the thyreoid tissue. In a number of cases, however, in which structural details are recorded, the association of the metastatic deposits with areas of abnormal thyreoid tissue has been very striking. Attention is again directed to those cases which received special comment early in this paper. In Virchow's case of testicular tumour, the only sites of metastasis beyond the lungs were the sternum and an old nodular goitrous thyreoid. In Kaufmann's case of ovarian carcinoma, in Naegeli's case of rectal cancer, in Kettle's case of uterine carcinoma, in Sauer's case of chloroma, and in Prym's case of chorionepithelioma, the metastatic growths in the thyreoid were located in and restricted largely to adenomata, while the more normal thyreoid tissue was uninvolved. In Rost's case of "hypernephroma," a metastasis occupied an area of fibrous tissue in an old goitrous thyreoid. Accepting the metastatic character of Müller's case of haemangio-endothelioma, the metastasis in the thyreoid lay within an old fibrous adenoma. In the case described by Reinhart, chronic tuberculous thyreoiditis co-

existed with a metastasis from a lung carcinoma; and the author suggested that the presence of the tumour predisposed the gland to tuberculous infection. From Reinhart's description, however, it is apparent that the tuberculous disease in the thyreoid was not recent, exhibiting well developed tubercles and areas of fibrosis, and it is improbable that the multiple nodules of secondary growth antedated these chronic inflammatory changes. If, then, a causal relationship existed between the two processes, it is more probable that the tuberculous changes predisposed the organ to the establishment of the metastatic tumours, an interpretation the converse of that suggested by Reinhart.

In my own material, preëxisting abnormalities of the thyreoid tissue were a prominent feature. In Case II the gland exhibited extensive fibrosis and lymphocyte accumulation; in Cases III and VI, adenomatous, cystic and fibrotic changes were present throughout the organ, and several of the smallest chordoma metastases were situated within adenomatous areas. In Case VII the metastatic growth was located in an area of tissue which was the seat of old fibrosis and calcification. In Case IX the thyreoid tissue exhibited advanced fibrosis and adenomatous changes, and several of the metastatic nodules occupied adenomatous areas. In Case X both of the small metastases present lay within adenomata. Thus, in no less than six of my ten cases the metastatic growths present either exhibited a decided preference for adenomatous or fibrosed areas of thyreoid tissue, or else occurred in an organ which was the seat of universal retrograde changes decidedly exceeding normal limits. From the evidence afforded by these observations and with the several striking instances cited from the literature, I cannot avoid the conclusion that the normally slight susceptibility of thyreoid tissue to the development of metastatic growths is decidedly augmented by the presence of adenomatous and other retrograde structural changes in that tissue.

What factors might determine this predisposition of altered thyreoid tissue to metastatic growths? Two possibilities present themselves, (*a*) altered vascular conditions in adenomatous or other abnormal areas may favour the arrest of blood-borne emboli; or (*b*) structurally altered thyreoid tissue may be a chemically more favourable soil than normal tissue for the development of secondary neoplasms. These alternative hypotheses will be discussed briefly.

In support of the first hypothesis might be advanced the observations of Simpson (1913),[49] Monogenow (1913)[50] and others on the impoverished blood supply to thyreoid adenomata. The vascularity of adenomatous tissue is much less than that of normal thyreoid, and the vessels exhibit all grades of degenerative change. It might be argued, then, that the relatively poorly vascularised adenomata with their deteriorated vessels lack the "flushing" action obtaining in normal tissue, so that the effective lodgement of minute emboli is favoured. On the other hand, since the embolic influx into any tissue must be proportional to its blood supply, the diminished vascularity of adenomata necessarily reduces the chances of malignant fragments entering these parts of the organ. Hence while it is *possible* that vascular conditions in adenomatous thyreoid tissue may favour embolic arrest, it is also *certain* that these same conditions minimise the opportunities of embolic entry. Further, it is entirely an assumption that malignant emboli are in general so minute that differences in capillary calibre or velocity of blood flow in different tissues will influence to any great degree the chances of embolic lodgement. We know that the average diameter of the capillaries in various tissues is approximately equal to the diameter of a single red blood corpuscle and that the highly plastic red corpuscles frequently suffer great deformation in traversing the narrower capillaries (Krogh, 1929).[51] Malignant embolic fragments must be much less deformable than blood corpuscles, and their size must usually be much larger than that of a single erythrocyte; often, indeed, neoplastic emboli certainly consist not of single cells but of clumps of cells or of fragments of thrombus bearing malignant cells. Such fragments must certainly suffer arrest in the arterioles or capillaries of any tissue. For these reasons therefore it is improbable that vascular deterioration is the principal factor determining the different incidence of metastatic tumours in healthy and in altered thyreoid tissue.

The second hypothesis, that altered thyreoid tissue is more suitable than normal tissue as a nidus for malignant growth, is suggested by (*a*) the peculiar characters of the thyreoid parenchyma, which, with its large content of iodine-rich colloid, is a chemically unique tissue, and by (*b*) the high oxygenation of that tissue. Malignant cells have a relatively anaerobic metabolism (Warburg, 1930).[52] It is possible then that the thyreoid and other well arterialised tis-

sues are poor soils for malignant growth partly because of their high oxygen tension, while poorly oxygenated organs like the liver offer a metabolically more favourable nidus for the proliferation of arrested cancer cells. Now adenomatous and other retrograde changes result in atrophy of the thyreoid parenchyma and its replacement by poorly vascular fibrous tissue, and the increased vulnerability of adenomatous or fibrosed areas to malignant metastasis may be due to the partial loss of those parenchymatous and metabolic qualities which antagonise neoplastic development.

Some support for this hypothesis is afforded by consideration of the tumour types most frequently responsible for thyreoid metastases. Our review of 57 neoplasms has shown that, next to mammary cancer (15 cases), two relatively rare forms of malignant growth, melanoma (9 cases) and lung cancer (8 cases), were the most potent in producing metastatic deposits in the thyreoid gland, while many commoner neoplasms, *e. g.*, the alimentary carcinomata, are relatively ineffective in this respect. These observations strongly suggest that some metastasising neoplasms, notably melanoma and lung carcinoma, manifest a decidedly greater inherent capacity than others for colonising the thyreoid. It is difficult to see how the different incidence of thyreoid metastasis by different tumour-types can depend on any local vascular conditions in the organ. That it is determined rather by a variable metabolic relationship between thyreoid tissue and the various types of malignant elements which effect lodgement therein, appears much more probable. Some kinds of tumour cells, *e. g.*, those of melanoma suffering embolic arrest in the thyreoid gland, find their chemical environment suitable to continued extravascular multiplication, while to other kinds of malignant cells thyreoid tissue is an uncongenial soil, in which, therefore, these cell deposits become sterile. This sterility, however, is only relative, and continued proliferation of the malignant cells may ensue should they chance to lodge in an adenomatous or other abnormal area of the gland where retrograde processes have deprived the tissue somewhat of its inhospitable metabolic qualities.

Another striking point emerges on further consideration of those recorded cases in which thyreoid metastases have exhibited some notable association to other lesions of the organ. The responsible tumours in these cases were carcinoma of testis (Virchow), carcinoma of ovary (Kaufmann), carcinoma of rectum (Naegeli), carcinoma of

uterus (Kettle), chloroma (Sauer), carcinoma of lung (Reinhart), haemangio-endothelioma (Müller), "hypernephroma" (Rost), chorionepithelioma (Prym), carcinoma of rectum (my Case II), carcinoma of breast (Case III), chordoma (Case VI), carcinoma of stomach (Case VII), carcinoma of breast (Case IX) and carcinoma of skin (Case X). Observe that in these 14 cases, carcinoma of the lung is represented only once and melanoma not at all, despite our finding that, next to mammary cancer, these two forms of tumour are most frequently responsible for metastases in the thyreoid. It is notable in this respect that the only one of our own seven cases in which the thyreoid parenchyma was entirely healthy was one of melanoma, and this was also the case in other recorded examples of melanoma in which details are given concerning the thyreoid gland, those of Chalier and Bonnet, Mori, and Girdwood. Evidently then, those very tumour-types which possess a maximum propensity for colonising thyreoid tissue seldom exhibit any remarkable association with other abnormalities of that tissue; while, on the contrary, such notable associations are encountered frequently in the case of other growths which seldom produce metastases in the thyreoid. This strongly suggests that these latter growths find healthy thyreoid tissue an infertile nidus and hence tend to remain sterile therein, while such infertility is less in adenomatous and other diseased areas, which therefore are frequently present in association with metastases from neoplasms of small thyreoid-colonising capacity. These considerations confirm the predisposition of altered thyreoid tissue to metastasis, and support the metabolic rather than the vascular hypothesis regarding this predisposition.

In pondering these problems, it occurred to me that a study of other non-neoplastic embolic processes in the thyreoid tissue might shed light on the questions under discussion. Accordingly a search of the literature for records of pyaemic and other metastatic inflammatory lesions of the gland was made. Only one reference to the association of such a lesion with a thyreoid adenoma was discovered. Benelli (1912)[53] described a case of mycotic infection of the gastric mucous membrane. The thyreoid gland contained a metastatic mycotic abscess, and this was located within a thyreoid adenoma. This observation might appear at first to support the vascular rather than the metabolic hypothesis of the predisposition of adenomata to metastatic processes, but further consideration suggests an alterna-

tive and precisely opposite interpretation. Practical medicine recognises the curative influence of iodine in mycotic infections, and it is possible that in Benelli's case the mycotic organism found the iodine-deficient adenomatous tissue a more favourable soil than the normal iodine-rich parenchyma. This case indeed may be interpreted as actually illustrative of the biochemical conception of tissue predilection for metastatic development.

For the various reasons outlined above, I believe that the frequent association of secondary tumours in the thyreoid with other abnormalities of the organ is not to be explained as merely coincidental, but that structurally altered thyreoid tissue is indeed predisposed to metastatic developments, and that this predisposition depends on the chemical or metabolic qualities of the recipient tissues with respect to the requirements of malignant cells arrested therein. We return then to the view of Fuchs and Paget mentioned in our introduction. To adopt Paget's simile, malignant seed, though necessarily sown less lavishly in the altered than in the normal tissue, germinates more readily in the former.

ENDOCRINE DISTURBANCES OCCASIONED BY METASTASES IN THE THYREOID

Thyreoid deficiency resulting from neoplastic destruction of the thyreoid gland is exemplified by my Case V, reported in detail elsewhere. A remarkable observation made first by Hirschfeld (1906)[26] and later by Mori (1913)[31] is that exophthalmos, tachycardia, tremor and other thyreotoxic symptoms may result from a metastatic tumour in the thyreoid gland; Ewing (p. 949)[3] has observed the same event. In three such cases Mori found this organ to be the seat of colloid goitre with plentiful deeply staining secretion; while in another case of metastasis in the thyreoid without thyreotoxic symptoms the gland was poor in colloid. Mori concluded that the thyreotoxic state was due to excessive absorption of secretion from active thyreoid tissue subjected to mechanical pressure by the enlarging metastasis and its stroma. This conclusion appears to me to be based on inadequate data, and not to be supported by the observations of other writers. In many of the other cases reviewed in this paper colloid goitrous changes were recorded, and in my own material abundant colloid-rich tissue was present in Cases III, VI and VIII, yet no thyreotoxic symptoms had been present.

CONTIGUITY-INVASION OF THE THYREOID GLAND

Though strictly not falling within the scope of this paper, it is desirable to refer briefly to the phenomenon of direct invasion of the thyreoid gland by contiguous neoplasms. Primary tumours of the pharynx, larynx, oesophagus or thymus may infiltrate the thyreoid, and this event is a frequent finding in cases of extensive cervical glandular metastases from carcinoma of the lip, tongue and pharynx. In a series of 35 autopsy cases of epidermoid carcinoma of the head and neck [54] I found the thyreoid invaded by growth in nine cases. In one remarkable case of this kind [55] the extensive cervical metastases from a lingual cancer had almost completely destroyed the gland, and compensatory hyperplasia of an accessory lingual thyreoid had occurred.

Primary endothelioma of the cervical lymph nodes may invade the thyreoid gland, as in Flournoy's case (1907)[56]; and the same may be observed in Hodgkin's disease of the cervical region (Osler, 1885).[41] The writer has seen an enormous anaplastic carcinoma of the parotid gland, the peripheral extensions of which infiltrated the thyreoid; and malignant intrathoracic neoplasms may extend into the neck and directly invade this organ (Jacobs, 1927).[57]

Summary and Conclusions

1. Forty-seven collected records of metastatic growths in the thyreoid gland are reviewed, and ten personal cases are added and described.

2. Secondary tumours occur more frequently in the thyreoid than is generally recognised, and a plea is made for more thorough pathological examination of this organ in cases of malignant disease.

3. There are good grounds for believing that different types of tumours possess different intrinsic capacities for establishing metastases in the thyreoid, and that melanoma and lung carcinoma are the most potent in this respect.

4. There is strong evidence that adenomatous and other abnormal areas of thyreoid tissue are predisposed to the establishment of metastatic neoplasms, and that this predisposition depends on chemical or metabolic rather than on vascular changes in the altered tissues.

5. In the case of those neoplasms which display a maximum propensity for metastasising to the thyreoid (melanoma and lung can-

cer) notable association of the metastases with other abnormalities of the gland are observed only infrequently. Conversely, thyreoid metastases from growths of low thyreoid-colonising tendency exhibit remarkably frequent association with preëxisting abnormalities of the organ.

NOTE: I am indebted to Professor P. MacCallum of the Department of Pathology, Melbourne University, for his stimulating criticism and interest, and to members of the Honorary Staffs of the Austin and Alfred Hospitals, Melbourne, for their consent to my utilising the histories of the cases.

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DESCRIPTION OF PLATES

Plate 38

Fig. 1. Case II. Vertical sagittal section of the right lobe of the thyreoid showing the metastatic growth at the upper pole (A). The fibrotic condition of the gland elsewhere is evident. (Natural size.)

Fig. 2. Case II. Photomicrograph of the metastasis shown in Fig. 1. A clump of loosely aggregated anaplastic tumour cells, some of signet ring type, are seen amidst thyreoid parenchyma which exhibits lymphocyte accumulation. × 180.

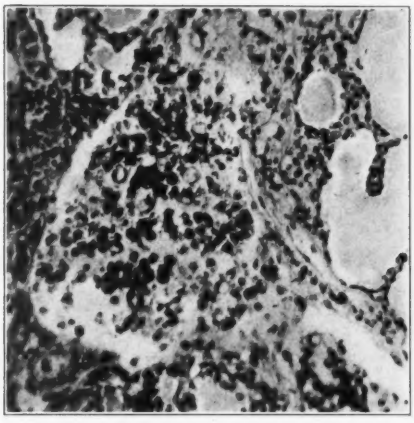
Fig. 3. Case III. Two sagittal sections of the right lobe of the thyreoid, showing the infiltrating metastatic growth, indicated by arrows. Observe the advanced adenomatous and cystic changes in the gland elsewhere. (Natural size.)

Fig. 4. Case III. Photomicrograph of the metastasis shown in Fig. 3. Mucoid adenocarcinoma is seen invading thyreoid tissue, which exhibits fibrosis, distortion of vesicles and aggregation of lymphocytes. × 80.

Fig. 5. Case III. Another area of the same growth, showing infiltrating carcinoma simplex. × 180.

Fig. 6. Case VI. Vertical sagittal section of the left lobe of the thyreoid, showing two translucent chordoma nodules denoted by arrows. Notice the conspicuous adenomatous, cystic and fibrous changes throughout the gland. (Natural size.)

1



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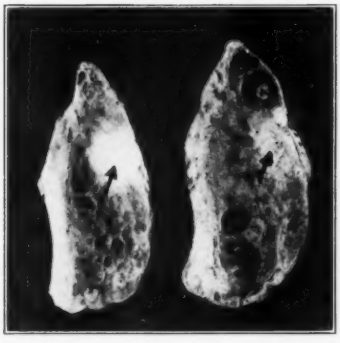

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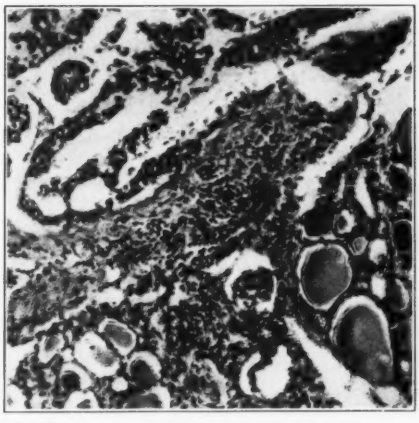

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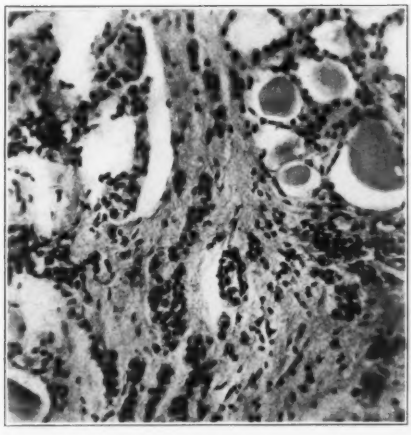

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6

Willis

Metastatic Tumours in Thyreoid Gland

PLATE 39

FIG. 7. Case VI. Photomicrograph of junction of thyreoid and chordomatous tissue. The latter stains deeply because of its high mucoid content. The thyreoid exhibits advanced fibrosis, lymphocyte accumulation and atrophy of the parenchyma. × 80.

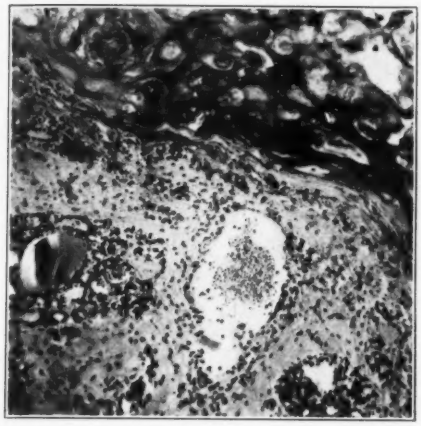
FIG. 8. Case VII. Photomicrograph from periphery of metastasis, showing thyreoid tissue penetrated by a large irregular acinus of adenocarcinoma. × 80.

FIG. 9. Case VIII. Vertical sagittal section of the right lobe of the thyreoid showing the irregular metastasis with satellite nodules in the caudal parts of the gland (A). (Natural size.)

FIG. 10. Case VIII. Photomicrograph showing the periphery of the clear-celled renal carcinoma invading thyreoid tissue. × 100.

FIG. 11. Case IX. Diffuse invasion of fibrosed thyreoid tissue by carcinoma simplex. × 60.

FIG. 12. Case X. Small adenoma of thyreoid containing a diffusely infiltrating metastasis denoted by the arrows. × 12.



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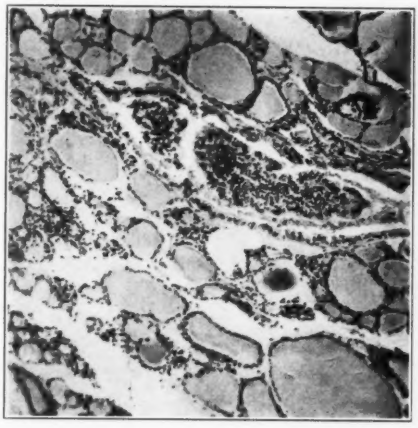

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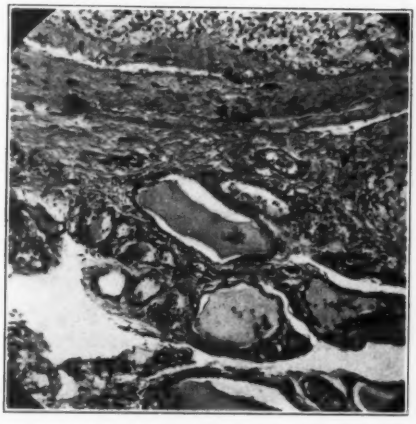

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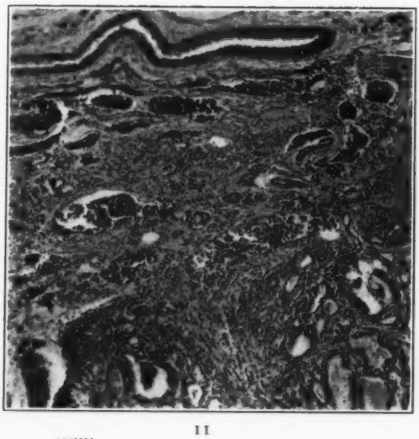

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12

Metastatic Tumours in Thyreoid Gland

THE SUSCEPTIBILITY OF THE CHORIO-ALLANTOIC MEMBRANE OF CHICK EMBRYOS TO INFECTION WITH THE FOWL-POX VIRUS *

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For studying a representative of the pox group of virus diseases, fowl-pox has many advantages, among them being the fact that infectious material is readily obtained and easily handled, since the disease is limited to fowls. It is believed that knowledge gained concerning this disease may be serviceable in the study of other members of the pox group. Hence, this virus has been the subject of several problems investigated in this laboratory during the last three years.

Fowl-pox, like the other pox diseases, is characterized by the appearance of eruptive skin lesions. The spontaneous fowl-pox nodules appear especially on the unfeathered parts of chickens, although experimental lesions may be easily induced in specialized epidermal structures such as cornea, feather follicles and oil gland. The lesions consist of a hyperplasia of the epithelial cells, with inclusion bodies in their cytoplasm. It has been shown that these inclusions are composed of groups or colonies of minute (Borrel) bodies.[1] While the presence of inclusions has always been considered pathognomonic of the disease, recent experimental work has given much evidence in favor of the theory that the Borrel body, one component of the inclusion, is the etiological agent of the disease.[2, 3, 4]

Heretofore, fowl-pox has been studied only in the grown or newly hatched chicks, or in tissue culture. Tissue culture experiments with this virus have, however, been few and inconclusive.[5, 6] The present paper deals with the inoculation of the virus into embryonic tissues in the incubating egg.

The chorio-allantoic membrane of the chick embryo has been used by a number of investigators for the study of the growth of various implanted tissues. Rous and Murphy [7] were the first to use

* Received for publication March 7, 1931.

this technique for the study of tumors. Danchakoff [8] has used the method to grow embryonic chick tissues. Since the publication of these two papers the technique has been used frequently in experiments with auto- and heteroplastic grafts, as well as in those with auto- and heterogeneous tumors. The production of experimental infection in the chorio-allantoic membrane has, however, been done only in the one instance where Rous and Murphy grew the virus of the Rous sarcoma.[7] *

Technique for Obtaining Sterile Virus

One of the most important steps in the technique of virus inoculations of embryonic chick membrane is the use of material free from contaminating microörganisms. The only methods available in the past for obtaining uncontaminated fowl-pox virus have involved considerable dilution of it, such as filtering through a Berkefeld candle or using the virus which capillary attraction has caused to rise higher than bacteria on a piece of filter paper.[9] The virus thus obtained is associated with the minute Borrel bodies in suspension. It was thought that some method which would provide uncontaminated virus consisting largely of inclusions would be especially useful. A number of such methods have been developed recently in connection with this work. Since each may prove advantageous for certain types of experiments, these will be described in detail before continuing with the experiments on embryo inoculation.

Method I. Uncontaminated virus can be obtained directly from fowl-pox nodules on the skin of a chick. The following technique proved to be the most satisfactory. After plucking the feathers from the heads of young chicks, 1 to 2 weeks old, virus was inoculated at three points about 1 cm. apart, to allow the development of separate nodules which could be removed by one stroke of the knife. Since nodules of more than seven days' development are likely to be invaded by pyogenic bacteria, the chick was sacrificed six or seven days after inoculation. The head was bathed with 95 per cent alcohol and allowed to dry. With a sterile cataract knife, a nodule was cut off rapidly at a level deep enough to obtain the

* Mention is made by Askanazy [15] of the production of tuberculous chicks by the infection of fertile eggs.

infected cores of most of the follicles. The severed nodule was placed epithelial surface down on a sterile glass slide, while, with a pair of fine curved forceps, the infected cores were forced out of the follicles from the cut surface. These small pieces were washed twice with sterile Tyrode's solution and stored at 4° C in a small amount of the same solution. One piece was tested in glucose yeast broth. If no bacterial growth was apparent within twenty-four hours, the remaining virus was made into a suspension for inoculation by grinding with a few drops of Tyrode's solution.

METHOD II. A second method for obtaining uncontaminated inclusions, and one which is especially useful for tissue culture experiments, was developed during work with the inoculation of single inclusions picked out with the Chambers microdissection apparatus.[2] For this work inclusions from lesions of seven to ten days' development were used. The tissue was digested with 1 per cent trypsin to free the inclusions. These were then carefully washed several times with sterile saline. Finally a single inclusion was picked up with a minute sterile pipette and deposited on a sterile cover slip. Though only a few such experiments were tried, plasma cultures with inclusions thus washed remained sterile in every instance. However, unless single inclusions are required, the first method is preferable because it is much less difficult and affords a larger amount of virus.

METHOD III. A third method which is useful when numbers of free inclusions are desired was developed in the course of experiments on the effect of 1 per cent potassium hydroxide on the virus.[4] Since the usual bacteria are destroyed after a few hours in 1 per cent potassium hydroxide, while fowl-pox virus, in the form of inclusion bodies, survives for at least twenty-four hours, we performed a number of experiments to see if virus free from contaminating microörganisms could actually be obtained after one day's treatment with potassium hydroxide. It was found that in highly contaminated pieces of fowl-pox tissue certain moulds, and occasionally a bacillus, persisted for three or more days in 1 per cent potassium hydroxide. After such a long period of treatment the strength of the virus is much diminished and may be completely destroyed. By using inclusions, freed from the tissue by tryptic digestion and carefully washed several times in sterile saline, the number of contaminating organisms was greatly diminished as shown by inoculation of

the material into glucose agar, and plating. Proceeding with sterile precautions throughout, it was found that after twenty-four hours in 1 per cent potassium hydroxide, agar plates containing 10 cc. of agar and 1 cc. of a suspension of the treated inclusion bodies usually showed no contamination. Occasionally, however, one or two colonies of a mould persisted. Inclusions freed to this degree from contaminating organisms could then be used for most types of experimental work, though they were less satisfactory than inclusions obtained by the two preceding methods.

METHOD IV. The fourth method for obtaining uncontaminated virus came as a natural development of the successful inoculation of embryonic chick membranes and will be described later. Methods I and IV provide for the production of virus which has never been in contact with bacteria, a fact which should make these virus preparations valuable in immunological experiments.

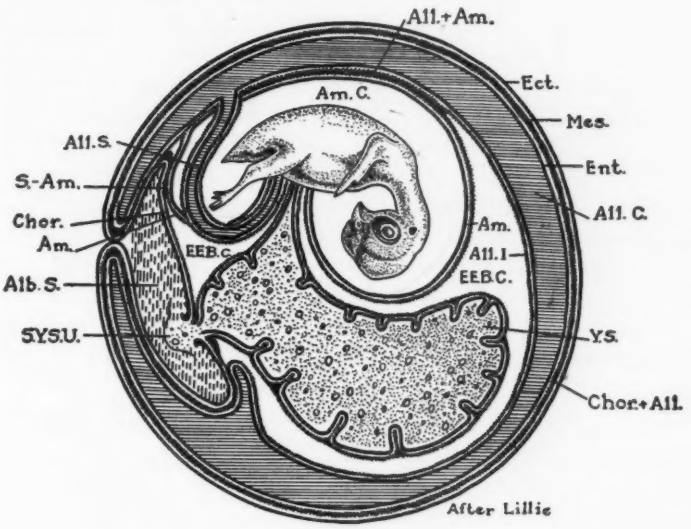
TECHNIQUE FOR INOCULATION OF CHICK EMBRYOS

The technique for opening the eggs used in our experiments was based on that described by Clark.[10] We omitted the use of a hot box, but kept the air sac immersed in water at 39° C. Keeping the air sac thus immersed prevented sagging of the egg contents when the egg was opened. We found that a piece of plasticene molded to fit the egg was a convenient support. The top surface of the egg was sterilized by bathing in alcohol and flaming. Then, proceeding with sterile precautions, a window, 7 to 10 mm. square was made by cutting or scraping with a sharp point. We found the sharp end of a scissors blade very convenient for this. After the shell was removed, the shell membrane was cut away carefully in order to expose the chorio-allantoic membrane.

For purposes of clarity in the description of the inoculation of chick embryos and the chorio-allantoic membrane, a diagram of the 12 day chick with its membranes has been reproduced from Lillie [11] (Text-Fig. 1). One label designating the chorio-allantoic membrane (the membrane formed by the fusion of chorion or serosa with the outer wall of the allantoic sac), has been added to the original diagram.

Two sorts of inoculation were attempted. The simpler procedure consisted in slightly injuring the chorio-allantoic membrane by

pricking with a needle and applying a drop of an uncontaminated virus suspension (Method I) to the injured area. In the second and more difficult operation, the skin of the embryo itself was inoculated. This involved cutting the chorio-allantoic membrane and amnion and slightly abrading the skin of the embryo, since some injury to epithelial cells favors the invasion of the virus.



TEXT-FIG. 1

Alb. S., albumin-sac. All. I., inner wall of the allantois. All. C., cavity of allantois. All. S., stalk of allantois. All. + Am., fusion of allantois and amnion. Chor. + All., fusion of chorion and outer wall of allantois. Am., amnion. Am. C., amniotic cavity. Chor., chorion. Ect., ectoderm. E.E.B.C., extra-embryonic body cavity. Ent., entoderm. Mes., mesoderm. S.-Am., sero-amniotic connection. S.Y.S.U., sac of the yolk-sac umbilicus. Y.S., yolk-sac.

In most of the techniques described in the literature the original piece of shell is replaced following the operative procedure and paraffined, so that the egg can be turned daily to continue normal development. Since we desired to watch the effects of the virus and to get sections at once if the chick should die, we substituted a glass cover slip for the original shell, fixing it upon a ring of vaseline, and returned the egg to the incubator immediately after the operation. This technique necessitated keeping the window uppermost during

the rest of embryonic growth. The lack of turning caused usually an oval depression and fold in the membrane directly below the opening. No other abnormality due to lack of turning appeared to occur, for a number of chicks hatched normally from eggs which had been subjected to this treatment.

Embryos at various stages of development were used. Since it takes about four days for a well defined fowl-pox lesion to appear after inoculation, it was necessary to inoculate at least that many days before hatching. The most extensive lesions were obtained six to seven days after inoculation, so that 10 to 15 day embryos were used most frequently. Occasionally, a contamination occurred in the inoculation of the egg. Sometimes a mould grew symbiotically with the virus in the embryonic membrane. Such contaminated eggs were discarded. Except as a contaminating organism is introduced upon inoculation, the eggs are relatively free from infection and remain, according to Rettger,[12] a sterile medium, unless subjected to moisture and dirt.

Results of Inoculation of Embryo Chick and Membranes

Fowl-pox infection of the chorio-allantoic membrane occurred as the result of inoculation in every case where the embryo survived for at least four days. Infections were first noted when thickened areas on the chorio-allantoic membrane were detected after several days' incubation. That a fowl-pox infection was definitely present was proved by three tests. The tissue, removed with sterile precautions and inoculated onto the scarified epithelium of adult hens, produced a massive fowl-pox lesion. Smears of the lesions, stained by Morosow's method,[13] showed Borrel bodies present in great numbers. Histological sections of the tissue showed the typical picture of the fowl-pox lesion (Figs. 2 and 9). These lesions are characterized by a marked hyperplasia of the ectodermal layer and an accompanying thickening of mesoderm as well. (Compare with normal membrane (Fig. 1).) Frequently hyperplasia of the entoderm occurs also. In the cells of the ectodermal layer many large inclusions are present, while in the entodermal layer, when occasionally a definite infection is present, inclusions are few and small. The lack of an inflammatory exudate, even in an advanced stage of the infection, should be noted.

In order to show the gross appearance of the infected areas several infected eggs were fixed in Zenker's fluid with the membranes intact. Sometimes the infection occurred in just a few areas, presumably at the site of the original inoculation (Fig. 6), but more often the infected area covered half the surface of the serosa (Fig. 5), and frequently small isolated areas of infection were found at a distance from the large primary lesion.

Upon the discovery that the outer embryonic membrane always developed this large area of infection directly below the window in the egg, it was decided to attempt the removal, with sterile precautions, of pieces of the infected membrane. By flaming the whole egg and carefully removing the coverslip, the infected tissue was exposed. Pieces of the infected membrane were cut away and washed in sterile Tyrode's solution. A sample of the tissue was inoculated into glucose yeast broth, and it was found that uncontaminated material could be obtained readily in most cases. The infected tissue in Tyrode's solution was then stored at 4° C until needed. Virus thus prepared was used generally within two weeks, although samples stored for several months were shown to be still virulent. Uncontaminated virus was obtained by this fourth method in much larger quantities than any other means so far devised. Consequently this method was used in subsequent experiments where such virus was required. The virus obtained by Method IV is convenient for almost any type of fowl-pox problem, if uncontaminated virus is needed, for the material can be used in a number of ways — as bits of infected tissue, as free inclusions which can be teased out from it, or as a Borrel body suspension, made by grinding the tissue with saline.

The inoculation of the embryonic skin caused considerably more trauma than the inoculation of the chorio-allantoic membrane. The percentage mortality was so great that this operation was soon abandoned, since the membrane inoculations proved very satisfactory. Several successful embryo inoculations were made, however. One infection of an embryo foot was produced (Fig. 7), and other infections were obtained, notably at the umbilicus. Although it was not intended to inoculate at this point, injury to the umbilical region must have occurred during the operation, for, with the inoculation of chorio-allantoic membrane alone, umbilical lesions were not obtained except on chicks which hatched and survived for several days.

Concerning the effect of fowl-pox on embryonic development and ability to hatch, our information is scant since most of the embryos were sacrificed before hatching. A few chicks, however, were hatched from eggs with infected membranes. These chicks were apparently normal, though they must have carried the virus, since all of those that were not sacrificed immediately developed fowl-pox lesions six to eight days later. The nodules appeared most frequently at the base of the beak or about the umbilicus. This infection may have been the result of autoinoculation during the process of pecking through the shell and escaping from the infected membranes. A second possibility is that the cells at the beak and umbilicus, injured during hatching, were infected by virus in the blood stream. The extreme vascularity of the chorio-allantoic membrane would make it seem highly improbable that the blood would remain virus free. Proof of the presence of virus in the circulation was obtained from a series of experiments in which pieces of liver were removed with sterile precautions from chicks which had either hatched from or died in eggs with infected membranes. In the majority of cases where liver material was inoculated onto the scarified epithelium of chicks a small lesion was obtained. In one case out of six, the inoculation of liver material produced no lesion. The lack of massive lesions as a result of these inoculations seemed to us to indicate that though the virus is present in small quantities in the blood stream, it is not actively proliferating there. This observation is in accordance with an accepted view concerning the virus present in the circulation of infected adult hens.[14]

Following the successful inoculation of the membranes of 10 to 15 day embryos, the question arose as to how early in the development of the embryo a successful inoculation could be made. Danchakoff [8] working with embryonic grafts on the allantois states that embryos younger than 7 days could not be used because of the small size of the allantois at that stage. Whether or not the absence of the chorio-allantoic membrane made our inoculations of membranes of embryos younger than 6 days more difficult, it was found that such inoculations were not generally successful. The chorio-allantoic membrane of 6 day embryos was infected with no difficulty, and on one occasion we succeeded in infecting this membrane in an embryo which was inoculated at the 4 day stage (Fig. 8). In younger embryos, the injury caused by opening the egg and pricking the membranes seemed to be greater, for the embryos usually died too soon

after inoculation for a lesion to develop. The technical difficulties involved caused us to abandon an attempt to determine the susceptibility of embryos of less than 4 days' development. It is not intended, therefore, to imply that younger embryos could not be infected.

Detailed study of a number of histological sections of infected chorio-allantoic membrane revealed the fact that entodermal as well as ectodermal epithelium could be infected. Inclusion bodies were usually less numerous, and hyperplasia was less marked than in infected ectoderm (Figs. 9, 10 and 11). Entoderm seems to be much less susceptible than ectoderm since entodermal infection did not occur in every case of successful ectodermal infection. A somewhat similar retarded response of entoderm was found by Huxley and Murray in work with chorio-allantoic grafts.[15] The stimulus in this case, however, was an operative one rather than one caused by an infection.

It should be mentioned in passing that occasionally the membrane was torn at inoculation, and at this point infected ectodermal cells had fused with cells of the entodermal layer. For the identification of a true entodermal infection, however, we were able to obtain sections of isolated nodules at a distance from the point of inoculation, where there was no possibility of ectodermal cells being present in the entodermal layer.

A further indication that entoderm is less susceptible than ectoderm to fowl-pox infection is seen in the fact that entodermal derivatives of the adult hen are rarely infected. Instances of spontaneous lesions in the crop have occasionally been observed. Two instances of spontaneous lesions of the trachea have also been seen. These lesions were not isolated nodules, but part of massive lesions of the throat. Though the infected areas appeared to be in columnar epithelium, the lesions were not considered to be complete proof of the susceptibility of tracheal epithelium (*i.e.* epithelium of entodermal origin), since they were not isolated from epithelium of ectodermal derivation. Using uncontaminated virus (Method IV), an attempt to corroborate the experimental infection of embryonic entoderm by the production of a fowl-pox lesion in adult tracheas was made.

With sterile precautions, the tracheas of two hens were cut, scarified and inoculated. The hens were sacrificed eleven and thirteen days respectively after inoculation. In both cases a gross infection

of the skin of the neck occurred but there were no adhesions to the trachea. In each experiment the mucous membrane of the trachea contained a number of small nodules, sections of which showed the typical fowl-pox lesion (Figs. 12 and 13). The infection of entodermal tissues, both adult and embryonic, is thus shown to be possible under experimental conditions. Uncontaminated virus may prove useful in other experiments of this type. Using such virus, intracerebral inoculations might prove interesting, as well as further inoculations of entodermal derivatives such as the mucous membrane of the intestine, or of mesodermal epithelium, *e.g.*, that in the kidney.

The position of the capillaries in some of the sections of infected chorio-allantoic membrane corroborates Danchakoff's theory concerning the development of the respiratory net of the allantois.[16] The allantois is both the respiratory and excretory organ of the embryo. By the thirteenth to fifteenth day its capillary network has in some manner become the outermost layer of living cells. This is contrary to the usual belief that the mesodermal cells of the embryo must always be bounded by two germ layers. This phenomenon was explained by Füllborn [17] as being due to the degeneration of the epithelial cells of the chorion. Danchakoff, however, holds that the final position of the capillary net is due to a migration of the capillaries. She proved that ectodermal cells were still present, by subjecting them to the pressure of grafted tissue, after which keratinization occurred.

Our sections indicate that migration of capillaries rather than degeneration of epithelial cells has occurred in the change of position of the respiratory net. The ectodermal layer can be distinguished because of the infected epithelium in at least part of the section. If the fowl-pox lesion had developed before the migration of the capillary net, this migration was prevented either wholly or partially. Some sections (Fig. 2) show the capillary net entirely below the ectoderm in the heavily infected area, while it occupies a midplace in the ectoderm of the same lesion where the infection is less (Fig. 3), and is found on the surface with ectodermal cells below when it reaches a non-infected area (Fig. 4).

In a number of the sections of infected serosa, epithelial pearls were noted, suggesting the possibility that rapid passage of the infection from one embryo to another might result in massive hyper-

plasia resembling an epithelial tumor. Accordingly a series of experiments was begun in which it was attempted to graft bits of infected tissue from the chorio-allantoic membrane on normal membranes. After a period of four to seven days, the original explant plus the newly infected area surrounding it was removed. Part of the block was used for sections and part for transplantation. The explants varied in size from 0.5 to 1.5 c.mm. It was found that identification of the transplant in the gross was difficult, due to its inclusion in the fresh growth of infected tissue. By dipping the transplants in a suspension of India ink in saline, however, enough carbon adhered to the tissue so that the transplant could be identified even after it had produced a heavy infection in the host membrane. Since it was thought that the ink might injure the cells of the transplant, both plain and inked transplants were tried, and several of each type were identified in sections. The series was terminated with the third transplant. Study of the sections obtained showed that in neither inked nor plain transplants had a true graft occurred. Apparently the infected cells degenerated too rapidly for them to become established in the new location. Though hyperplasia was evident, the type of lesion in the second and third transplants was not different from that obtained after the first inoculation. It was concluded that the epithelial pearls were probably due to mechanical displacement of the epithelium in the membrane.

Discussion

Experiments upon fowls have shown the great susceptibility of ectodermal cells to infection with the virus of fowl-pox. When the virus is injected intravenously the resulting lesions are almost entirely confined to the skin. Sometimes, however, the epithelium of the esophagus, crop and trachea are affected, showing the ability of the virus to multiply in epithelium having an entodermal derivation. From the fact of the infrequent occurrence of spontaneous gastro-intestinal and tracheal lesions, and from the characteristics of these lesions whether spontaneous or experimental, it seems evident that the virus of fowl-pox affects ectodermal epithelium much more readily than entodermal, and increases more abundantly in the former. In common with certain other cytotropic viruses, that of fowl-pox seems thus to possess a high degree of cellular specificity.

The experiments recorded in this paper show that the same specificity obtains when this virus is brought into contact with the tissues of chick embryos, and in similar degree. That is to say, in the embryo as in the adult fowl, ectodermal squamous epithelium is more susceptible, while entoderm of the allantois is less readily affected, and in the latter cells, virus regenerates much less abundantly, judging from the number and size of cellular inclusions.

This susceptibility appears very early in the cellular differentiation of the embryo. With the technical methods at our disposal it was not determined how early the embryonic cells acquire this susceptibility, or, to state it differently, how soon certain embryonic cells lose their susceptibility, supposing that the earliest undifferentiated cells from the ovum are all susceptible to the virus. It would be of great interest to know whether or not ectodermal and entodermal epithelium acquire their susceptibility as a result of cellular differentiation.

By the use of the chorio-allantoic membrane of chick embryos for the production of the infection, the preparation of non-contaminated concentrated virus in fairly large quantities is made possible. This virus, being the infected tissue grown in and obtained from a sterile medium, can thus be used in whatever form desired, *i.e.*, as infected tissue, inclusion bodies, or a suspension of Borrel bodies. This method and also Method I, described in this paper, have an advantage over any other known preparations of non-contaminated fowl-pox virus, in that, since the cells in which the virus has developed have never been contaminated, the virus should be free from antigens not directly associated with the disease. This fact should make it especially useful in immunological experiments.

One of the uses of such a virus preparation has been demonstrated in the successful inoculation of adult chicken trachea with fowl-pox virus. Inoculations of such virus into the internal organs of the chicken, especially those with epithelial surfaces such as the kidney, might give valuable information.

The use of embryonic chick membranes as a medium for the production of other virus infections, *e.g.*, vaccinia, might prove advantageous in the study of the etiology and development of these diseases.

Summary

1. Ectodermal and entodermal cells of the chorio-allantoic membrane of the chick, as well as embryonic chick skin, are susceptible to infection with the virus of fowl-pox at an early stage in the development of the embryo. Whether or not this specific susceptibility is acquired as a result of cellular differentiation has not been determined.

2. Four methods for the isolation of uncontaminated fowl-pox virus are described.

3. In two of these methods the virus is developed in tissue that has never been contaminated by extraneous microörganisms.

4. Fowl-pox infection in the trachea of the adult hen has been induced by means of inoculation with uncontaminated virus.

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DESCRIPTION OF PLATES

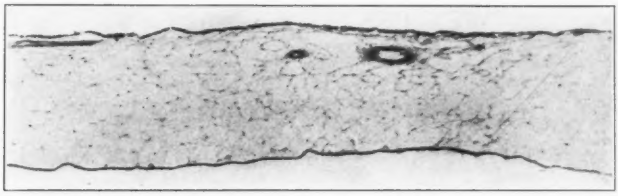
Plate 40

Fig. 1. Normal chorio-allantoic membrane from hatching chick. × 50.

Fig. 2. Ectoderm of chorio-allantoic membrane of chick embryo showing fowl-pox infection, and the position of the capillary net below a heavily infected area. Section taken five days after inoculation. Note absence of inflammatory exudate. × 200.

Fig. 3. An intermediate position of capillary net in the hyperplastic ectodermal epithelium adjacent to massive fowl-pox infection of embryonic membrane (Fig. 2). × 200.

Fig. 4. Position of capillaries on surface of non-infected ectoderm adjacent to area (Fig. 3) of hyperplastic epithelium in fowl-pox infected membrane. × 200.



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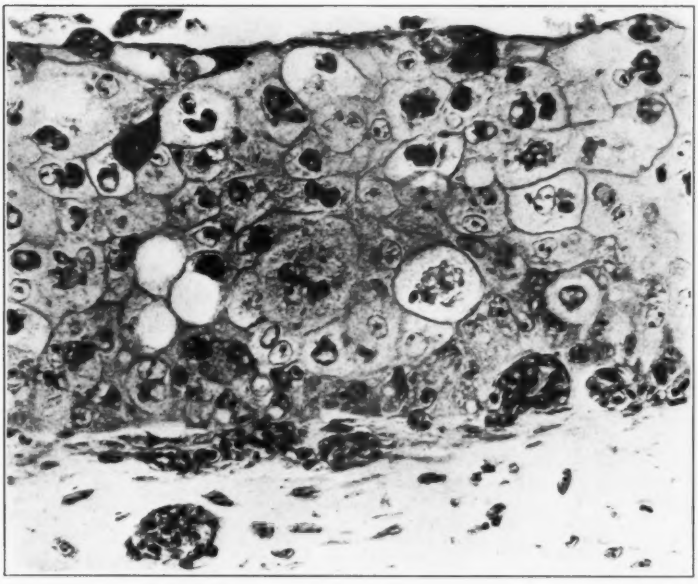

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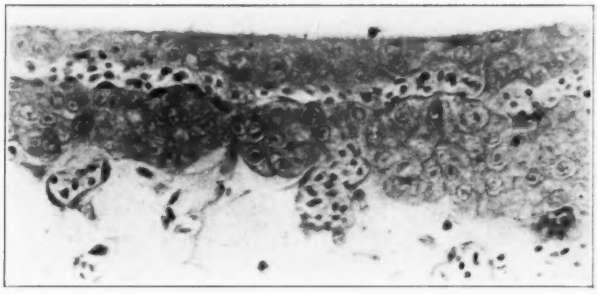

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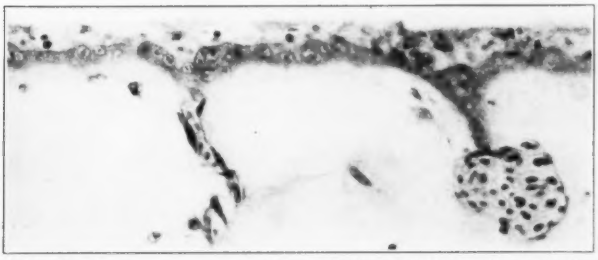

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Plate 41

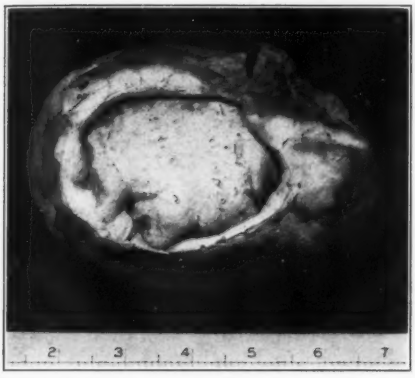
Fig. 5. Massive fowl-pox infection in chorio-allantoic membrane of 15 day embryo, seven days after inoculation.

Fig. 6. Isolated areas of fowl-pox infection in chorio-allantoic membrane of 16 day embryo, seven days after inoculation (shown at right).

Fig. 7. Fowl-pox infection in epithelium of foot of 21 day embryo, seven days after inoculation. × 50.

Fig. 8. Fowl-pox infection in ectoderm of chorio-allantoic membrane resulting from inoculation at 4 day stage. × 50.

Fig. 9. Fowl-pox infection in chorio-allantoic membrane showing massive lesion in ectoderm and hyperplasia of entoderm. × 50.



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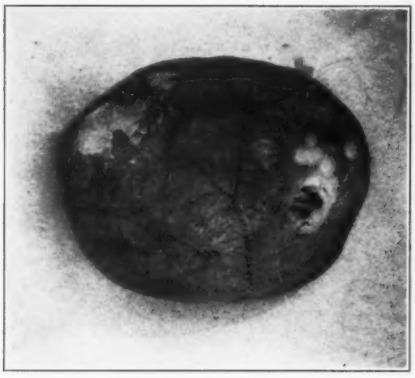

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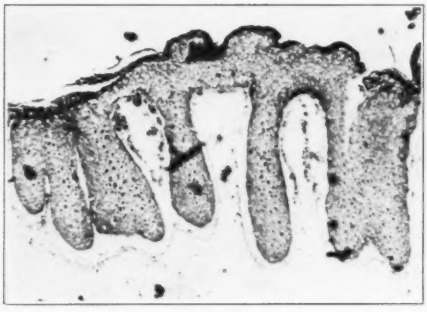

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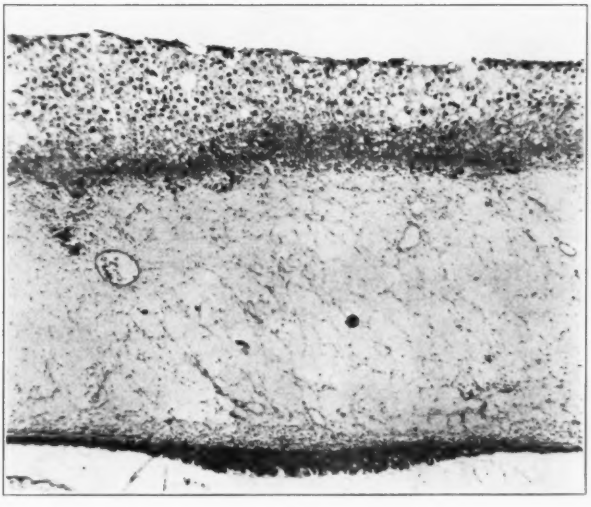

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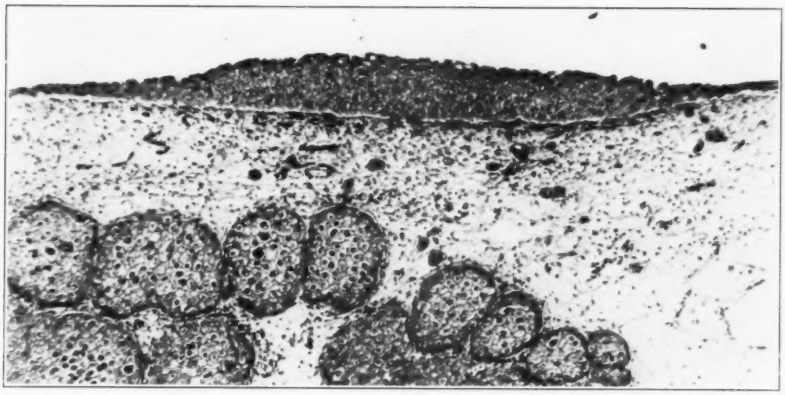
PLATE 42

FIG. 10. Isolated area of fowl-pox infection in entoderm of chorio-allantoic membrane, six days after inoculation. Note small size of inclusions and cells as compared with those of epithelial nodules from ectodermal layer in lower portion of picture. × 50.

FIG. 11. A portion of Fig. 10 under higher magnification, showing fowl-pox infection in entoderm of chorio-allantoic membrane. Note that inclusions are smaller and hyperplasia less than in infected ectoderm of Fig. 2. × 200.

FIG. 12. Experimental fowl-pox infection of mucous membrane of trachea. *Cf.* normal epithelium at left with infected area at right. × 50.

FIG. 13. A portion of Fig. 12 under higher magnification, showing experimental fowl-pox infection of mucous membrane of trachea. Note metaplasia of epithelium and relatively few inclusions. × 200.



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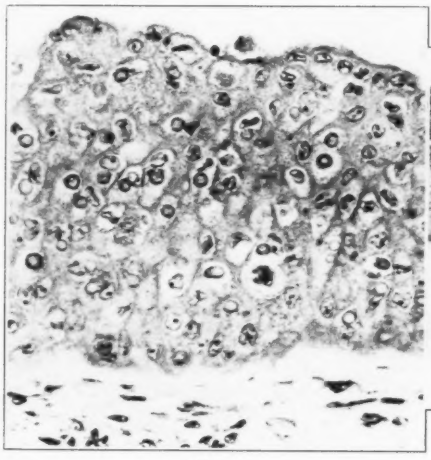

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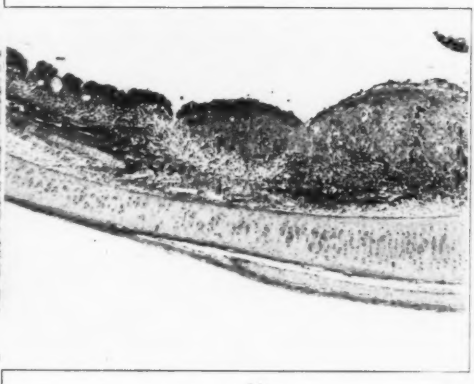

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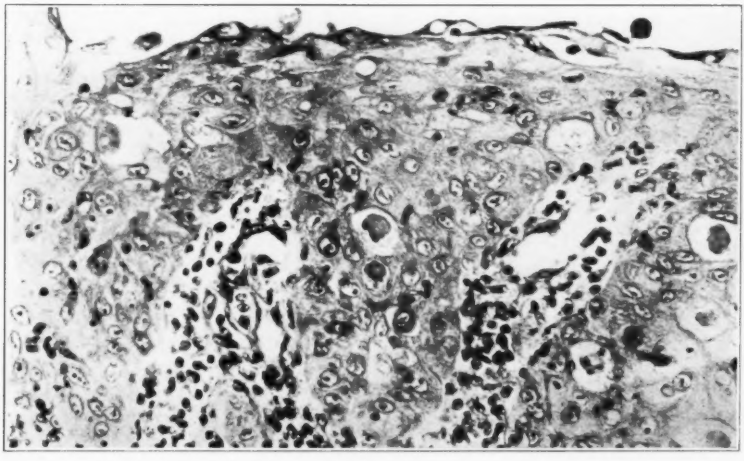

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Woodruff and Goodpasture Susceptibility of Chick Embryos to Fowl-Pox Virus

SPONTANEOUS RUPTURE OF THE HEART*

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As Beresford and Earl [1] state in a recent report: "The literature on the subject (of spontaneous cardiac rupture) consists mainly of a large number of reports of isolated cases, or very small series, published frequently by quite unskilled observers, struck by the dramatic aspect of the condition." These authors report upon 46 cases of heart rupture among inmates of an insane hospital. Only 14 of the more recent ones had been studied with care histologically, but every one of this number showed recent infarction. Autopsies of the other 32 cases made no mention of infarction, such changes as fatty, friable, soft and degenerated being recorded. This indicates how unreliable opinions as to the cause of the rupture undoubtedly are when made without microscopic examination of the tissues, as many of the 32 cases must have shown infarction which was overlooked because microscopic sections were not prepared.

Krumbhaar and Crowell,[2] and Davenport [3] have reported small series of cases and reviewed the literature, collecting in all over 600 reported cases. They likewise mention the dearth of well studied cases, and bring up several of the unsettled questions in regard to the causes and incidence of rupture. To answer these questions all cases occurring should be studied carefully by the pathologist in an attempt to reconstruct the sequence of events leading to the rupture.

The heart studied in this case was removed by Dr. C. W. Duval at a private autopsy and was kindly turned over to me to be reported.

REPORT OF CASE

Clinical History: A man of 65 years, in apparent good health, with no history of previous disturbances of circulation fell dead while walking upon the street. An autopsy was performed within three hours after death.

*Received for publication March 2, 1931.

Gross Findings at Postmortem Examination: On opening the thorax the most prominent feature was the ballooned-up pericardial sac which contained more than a liter of blood. The heart showed an excessive amount of subepicardial fat, particularly over the apex, and the surface of the muscle displayed parallel streaks of yellow, alternating with quite normally colored muscle.

On seeking for the source of the blood in the pericardial sac it was found that there was a rupture about 4 cm. in length in the posterior aspect of the left ventricle near the interventricular groove and somewhat tangential to it, the course of the rupture lying roughly parallel, and about half an inch toward the groove, from the small coronary artery on the posterior of the left ventricle (Fig. 1). This artery (D), which largely supplied the area in which the rupture occurred, was somewhat of an anomaly in that the larger branch in this instance came from the right coronary and the smaller anastomosing branch came from the left coronary, which is the reverse of normal.

The rupture showed ragged edges and a gaping slit. The heart was removed and placed in formalin for careful study.

The right auricular appendage contained a thrombus adhering to the lateral wall. The muscle under the thrombus was grayish and translucent. A small branch of the right coronary supplying this area was thrombosed.

In the lateral wall of the right ventricle, just under the tricuspid valve, was another thrombus firmly adherent and of a reddish gray color. Section of the musculature under this thrombus disclosed an area about 3 cm. wide and 5 cm. long, lying just along the margo acutus, which was dark grayish and translucent. The black color of a portion of the center indicated hemorrhage into the area. The artery to this part of the heart was likewise filled with a thrombus. No abnormality of the tricuspid and pulmonary valves was noted.

The left auricular appendage contained no clot and was normal in appearance. The mitral valve showed an irregular calcareous area on the left leaflet, otherwise no pathological changes were noted. The chordae tendineae were normal. The muscle tissue around the rupture was dark, almost black from degenerative changes and altered blood from hemorrhage into the tissues. Adjacent to this darkened muscle there were irregular, grayish, translucent areas throughout a space at least 6 cm. along the interventricular groove

and extending about 4 cm. from the groove into the wall of the left ventricle. The muscle was most changed deep in the wall and appeared more normal toward the endocardium and epicardium. Two large calcareous plaques were found in the aorta just beyond the aortic valves. The valves themselves were normal in appearance.

Interest of course centered in the coronary arteries. The left was rigid and stiff for 4 cm. from the aortic opening. The anterior descending branch was rough and nodular almost to the apex, and on cut section the knife struck hard gritty areas.

The opening of the right coronary artery into the aorta was much constricted, and beginning about 4 mm. from this opening there was an ante mortem clot filling the artery and all of its earlier branches. However, the thrombus did not extend down into the artery supplying the area near the rupture beyond the place where the anastomosing branch from the left coronary joined it, but there was another thrombus filling the distal portion of this artery and its finer branches. In other words, there was no blood or thrombus in this artery between the anastomosing branch of the left coronary and the upper end of the rupture (see portion marked "empty," artery D, Fig. 1).

Microscopic Findings

Left Coronary Artery: Sections made at various intervals throughout the course of this artery and its branches showed tremendous thickening of the walls, with advanced degenerative changes. A section taken near the aorta (Fig. 2) is illustrative of the condition of the larger branches. A deep plaque, covering most of the circumference of the vessel, had undergone degeneration to such an extent that no cells were recognizable and various areas contained the slit-like openings left when the cholesterol and other fatty substances were dissolved out; the outer margin of the whole plaque showed considerable infiltration of calcium. The lumen of the vessel was greatly narrowed. Even the smaller branches, such as the terminations of the anterior descending branch (Fig. 3) showed thickening and degenerative changes.

Right Coronary Artery: Sections from near the aorta showed the lumen to be very narrow and filled with a thrombus of recent formation. The condition of the walls was quite similar to that of the left coronary, as described above, except that degenerative changes

were so advanced that satisfactory sections for photographing were not obtained. All of the larger branches exhibited marked changes such as those seen in Fig. 4. Even the small branches, such as those immediately above the rupture (Fig. 5), displayed such pathological changes as intimal thickening and hyaline degeneration.

Myocardium: In sections from an area in the left ventricle near the rupture grossly described as gray and translucent, about midway between the endocardium and epicardium, there was complete degeneration of large groups of muscle fibers, with many fibroblasts growing into such areas (Figs. 6 and 7).

Sections taken at the border of the rupture disclosed a somewhat different pathology. The fibers nearest the rupture had lost their nuclei and had become bright red-staining and homogeneous. A little further away the fibers were likewise without nuclei, but their cytoplasm was coarsely granular. Throughout these areas of hyaline degeneration and cloudy swelling the fibers were widely separated by granular precipitate and leucocytes, principally neutrophiles (Figs. 8 and 9).

The muscle under the thrombi in the right auricle and right ventricle also showed marked changes. Large groups of fibers were hyalinized and stained bright red with eosin. Fibers around these showed pronounced fatty degeneration, while those nearest the endocardium exhibited only granular degeneration. One section from the area in the right ventricle contained large groups of fibers almost completely degenerated, and fibroblasts were beginning to infiltrate between them.

Sections of muscle taken from the left ventricle some distance from the rupture, in what appeared to be normal tissue, did not show very much pathology. The spaces between some of the fibers were widened in places and filled with a fine granular precipitate. There were a few minute clear-cut vacuoles in some of the fibers. Except for this slight edema and fatty degeneration the only other change noted in the myocardium was hypertrophy.

Discussion

This case bears out the claim made by Beresford and Earl that rupture usually occurs in an infarcted area, frequently the result of coronary disease and precipitated by coronary thrombosis or embolism.

It is difficult to decide what the sequence of events was in this case, but it appears to have been as follows: The small branches supplying the infarcted areas in the right and left ventricles seem to have been the site of thrombosis or embolism from atheromatous material some days before the rupture, as evidenced by the beginning of repair in the areas supplied by them. It is likely that the vessel supplying the lateral portion of the right auricle became thrombosed shortly afterward. A propagating thrombus then began to form in the right coronary itself (Fig. 1, artery (A)), gradually extending down until it reached the posterior descending branch (C) which runs along the interventricular groove, further cutting off the nutrition to the infarcted area in the left ventricle. When the thrombus finally reached the junction of the terminal branch (D) of the right coronary and the anastomosing branch (E) of the left coronary, nutrition was finally completely cut off from this large area and it became so softened that rupture took place.

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DESCRIPTION OF PLATE

PLATE 43

FIG. 1. Posterior aspect of heart showing rupture in left ventricle.

FIG. 2. Section of left coronary artery near aorta. Note marked thickening of intima, undergoing degeneration and calcification.

FIG. 3. Section of smaller branch of same, showing that the arteriosclerosis extends into the terminal branches.

FIG. 4. Section of right coronary artery about 6 cm. from the aorta. Note the thrombus in the lumen and the degenerative changes in the wall.

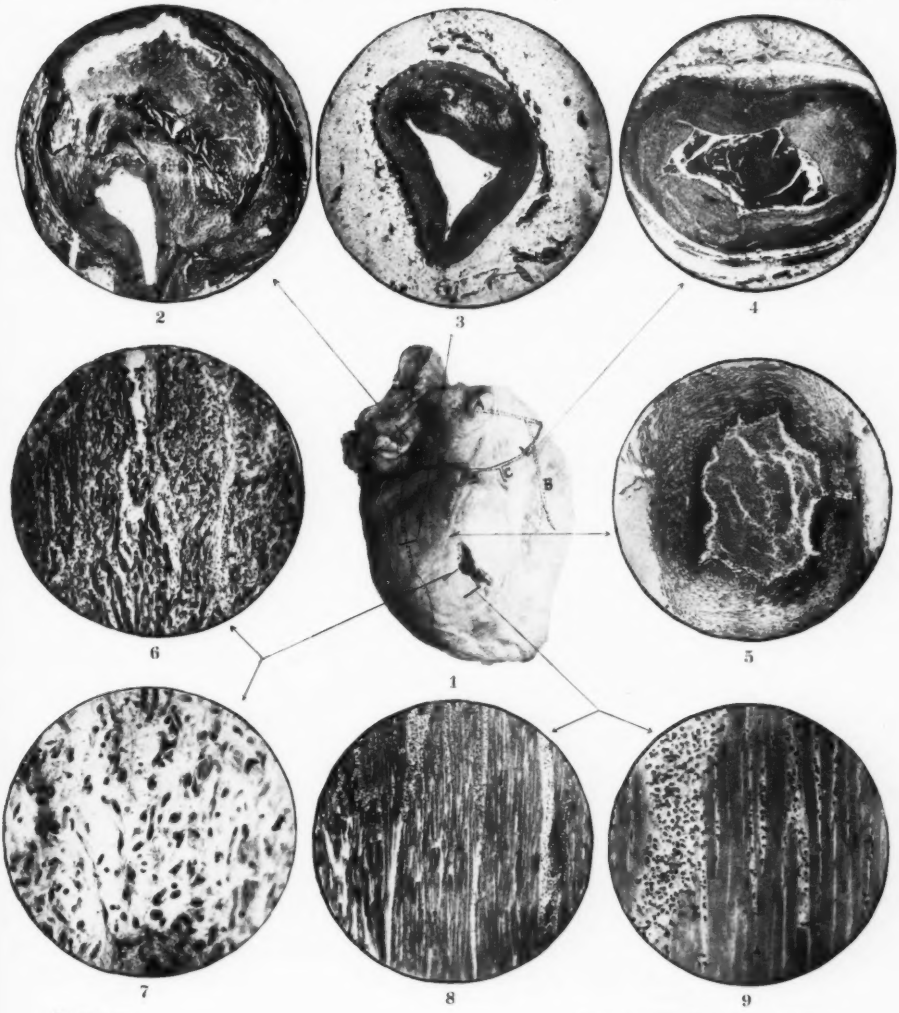
FIG. 5. Section of small branch of same just above the rupture.

FIG. 6. Section of myocardium near the rupture, showing disappearance of groups of fibers and newly formed connective tissue.

FIG. 7. Higher magnification of a field of Fig. 6.

FIG. 8. Section of myocardium at the edge of the rupture, showing various types of degenerative processes and leucocytic infiltration.

FIG. 9. Higher magnification of a field of Fig. 8.



Feemster

Spontaneous Rupture of Heart

CONGENITAL HEART DISEASE *

A Persistent Ostium Atrioventriculare Commune with Septal Defects in a Mongolian Idiot

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A defect of the adjoining portions of the interauricular and interventricular septa with a common auriculoventricular orifice is an unusual cardiac anomaly. In 1927 Gunn and Dieckmann [1] reported two such cases, both occurring in Mongolian idiots. They were able to find six cases previously described in the literature and quote Keith as stating that he had seen fourteen and as citing two more, making a total of twenty-two such cases which they found described or referred to in the literature prior to their report. However, Keith [2] did not describe his cases, but simply stated that he had seen fourteen hearts with common auriculoventricular orifices and that this condition was always associated with other grave defects, such as pulmonary stenosis or transposition of the great vessels. Neither of Gunn and Dieckmann's cases had any associated major defect (one had a patent foramen ovale and a patent ductus arteriosus), and of the six cases which they found described in the literature only two showed associated defects, namely a bicuspid pulmonic valve in one and a partial transposition of the aorta in another. Mönckeberg [3] also described a case, not included in those found by Gunn and Dieckmann, which showed no associated defect other than a small patent foramen ovale. From this it is evident that a common auriculoventricular orifice and septal defects, uncomplicated by other grave anomalies, is of rare occurrence.

Report of Case

Clinical History: The patient was a white female who died of scarlet fever at the age of 4 years and 9 months. The three older children of the family were normal. This child was extremely cyanotic at birth, although it was a full-term baby with a normal labor and easy low forceps delivery. At birth a loud systolic

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murmur was noted over the base of the heart. The heart seemed to be enlarged, and a thoracic X-ray taken the day after birth revealed an enlarged thymus. The thymus decreased in size under X-ray therapy and the cyanosis gradually subsided. However, during the early months of life great difficulty in feeding was experienced. Within two months after birth the child was recognized as a Mongolian idiot, the characteristic stigmata of this condition gradually developing.

Starting at the age of 6 months with an attack of bronchitis, the patient suffered from recurring pulmonary infections associated with severe cyanosis. Between these attacks cyanosis was absent. Death finally occurred in the course of a mild attack of scarlet fever, the patient, while seemingly in little danger, suddenly became extremely cyanotic and died within a few hours.

The cardiac condition was repeatedly studied during the life of the patient. The heart was definitely enlarged, especially to the right, so that it seemed more centrally located than usual. Over the base there was a loud blowing systolic murmur that was not transmitted to the great vessels. During the attacks of cyanosis which accompanied respiratory infections, this murmur increased in magnitude. Exertion never was a factor of importance because the child was inactive. At the age of 2 years she learned to stand, while holding to something, but never was able to walk independently.

Description of Heart

The heart, while normal in shape, is greatly hypertrophied, weighing 183 gm. (normal for age about 80 gm.),[4] and shows a slight dilatation of all chambers. The right ventricular wall approximates the left in thickness, the right measuring 13 mm. and the left 14 mm. in width. Both auricular walls are moderately thickened. The interauricular septum is complete above and shows a normal fossa ovalis (Fig. 2). The septum is incomplete below, its crescentic free border arching over a large common auriculoventricular orifice to join its anterior and posterior margins at the base of the auricles, thus forming a free communication between the two auricles (Fig. 2). This opening measures 1.6 cm. in anteroposterior diameter and 0.6 cm. in height. Above, it is bounded by the arching free border of the interauricular septum. Below, it is separated partially from the large defect of the interventricular septum by the incomplete diaphragm formed by the central segments of the common auriculoventricular valve. The free margin of the interventricular septum arches downward from the anterior and posterior margins of the auriculoventricular orifice to form an opening through which the two ventricles directly communicate (Figs. 3 and 4).

There is a single large auriculoventricular orifice which is slightly constricted in the middle (Fig. 1). The right half of this functions

as the right, and the left half as the left auriculoventricular orifice. This large orifice is guarded by a valve composed of five segments. There are two large mesial segments, one anterior and the other posterior, each lying half in the right and half in the left heart. The right halves of these two segments represent the septal segment of the tricuspid valve, while the left halves correspond to the aortic segment of the mitral valve. On the right there are two additional divisions — the normal anterior and posterior tricuspid segments. On the left a normal posterior mitral segment is present. The arrangement of the valve segments is illustrated in Fig. 1. The large posterior central segment is attached closely to the margin of the underlying interventricular septum by a group of partially fused, short, cord-like strands of connective tissue; thus there is very little communication between the ventricles in this location. Under the anterior central segment the defect of the interventricular septum is quite deep, this segment being attached to the margin of the defect by only one large branched chorda tendinea (Fig. 4).

The defect of the interventricular septum is continuous with the auricular defect, the two being separated only by the incomplete diaphragm formed by the large central segments of the auriculoventricular valve. Its anteroposterior diameter is the same as that of the defect of the interauricular septum (1.6 cm.). Its greatest depth is 0.6 cm. and this lies under the anterior central valve segment. The defect extends well forward under the aortic orfice on the left (Fig. 4). The opening into the right ventricle lies under the central valve segments, especially under the anterior one and behind the conus, which is quite thick-walled (Fig.3). The endocardium in this region is thickened and hyalinized. Several thickened chordae tendineae arise from this site, some of which pass into the left heart to be attached to the valve there. An especially large branching chorda arises from the free margin of the defect (Fig. 4). The remaining chordae are normal.

The orifice of the systemic aorta, which lies immediately above the anterior portion of the defect in the interventricular septum, is guarded by three normal cusps. It measures 4.5 cm. in circumference. The pulmonic orifice measures 5 cm. in circumference and also has three normal cusps. The systemic and pulmonic aortae are free from anomalies. The ductus arteriosus is not patent. It is represented by a fibrous cord connecting the two with a dimple-like

depression in the systemic aorta at the site of its attachment. The pulmonary artery and its branches are very large. The systemic aorta is 4 cm. in circumference, while the pulmonary artery measures 6.5 cm. Its branches are also large, the left 3 cm. and the right 4.5 cm. in circumference. The pulmonary artery shows several very small yellowish patches of atherosclerosis. None are present in the systemic aorta. The cavae, coronary sinus, and pulmonary veins are all normal and enter the auricles in the usual manner. The Eustachian valve is well formed.

Other positive findings at autopsy were a terminal bronchopneumonia and an interesting anomalous condition of the ovaries. Two small bodies, each about 6 mm. in diameter, were found attached to the posterior surfaces of the broad ligaments in the position normally occupied by the ovaries. Except for their small size they appeared to be normal ovaries. However, on microscopic examination they were found to be composed of a vascular and fibrous stroma containing a large number of tubular structures lined by high columnar epithelium, evidently vestigial wolffian tubules. A careful search of serial sections through each of these bodies revealed a complete absence of any ovarian follicles or germinal epithelium.

Discussion

The interpretation of this type of cardiac anomaly is extremely interesting, but is complicated by the uncertainty regarding the exact process by which the final complete separation of the two sides of the heart is accomplished normally. Particularly is this true in regard to the relative importance of the parts played by the septa and the endocardial cushions. Mönckeberg [5] believes that the septa play the larger part, the endocardial cushions growing out along the margins of the interauricular and interventricular septa when the septa reach the level of the auricular canal. He states that the presence of the margin of one or the other of these septa at the level of the auricular canal is a prerequisite for the fusion of the endocardial cushions, and that the absence of the margins of both septa at this level necessitates the persistence of the primitive single auriculoventricular orifice. From this it would follow that the primary fault in these cases is a growth deficiency in both the interauricular and the interventricular septa. Thus the common auriculo-

ventricular orifice is not due to any defective development inherent in the endocardial cushions, but results from the absence of a septal margin at the level of the auricular canal. On the other hand, Gunn and Dieckmann, following Mall, believe that the final closure of the ostium primum (primary interauricular foramen) and probably of the interventricular foramen is brought about by the fusion and growth of the endocardial cushions. They conclude, therefore, that the primary fault is a growth deficiency on the part of these structures. For a detailed discussion of this problem the reader is referred to the article by Gunn and Dieckmann.[1]

The author is inclined to believe that their position is the correct one. The careful work of Mall,[6] which is stressed by these authors, is especially convincing. Mall observed in a human embryo of 8 mm. the upward growth of the anterior and posterior endocardial cushions encroaching upon the ostium primum and uniting with the interauricular septum well above the auricular canal. This condition is clearly shown in Mall's illustrations. In an embryo of 9 mm. he found the endocardial cushions fused within the auricular canal, while the interventricular foramen was still open. In the case of this embryo he does not state whether or not the ostium primum was closed. This is strong evidence that the endocardial cushions play a very large part in the closure of the ostium primum and that they do fuse before the interauricular and interventricular septa reach the level of the auricular canal. In support of the opinion that a primary deficiency of growth on the part of the endocardial cushions is responsible, at least for the valvular anomaly and the defect in the lower part of the interauricular septum, is the fact that in cases of persistent ostium primum, uncomplicated by a defect at the base of the interventricular septum, there is commonly an associated anomaly of the valve segments, the aortic leaflet of the mitral valve being cleft from its free border to its insertion (Abbott [7]). This suggests that in such cases the fault may be in the endocardial cushions rather than in the development of the interauricular septum.

Gunn and Dieckmann also discuss in detail the defect of the base of the interventricular septum, concluding that there is little evidence in their cases that the interventricular septum was deficient; therefore the defect was due probably to a failure of downward growth of the endocardial cushions. Their reasoning applies with equal force to our case. In this connection, a case reported by

Abbott [8] seems to fill partly the gap between the cases of persistent ostium primum with deformed auriculoventricular valve segments, normal auriculoventricular orifices and intact interventricular septum, and the type of case we have reported. In Abbott's case the aortic segment of the mitral valve was not only cleft, but was completely divided and the upper part of the interventricular septum "appeared to be slightly defective below." As Gunn and Dieckmann point out, while embryologists are not agreed as to the exact mechanisms of the process, it is safe to assert that the final closure of the interventricular foramen is brought about by the fusion and growth of three structures, namely the bulbar septum, the interventricular septum, and the endocardial cushions. A deficiency in any one of these three could lead, therefore, to a defect in the base of the interventricular septum. We believe Abbott's case, mentioned above, to represent a slight defect of the interventricular wall brought about by a failure of downward growth of the endocardial cushions, and our case to represent a more severe defect originating in a similar manner.

To summarize this discussion, it is suggested that a persistent ostium primum with deformed valve segments is due to a failure on the part of the endocardial cushions to grow up and unite with the interauricular septum, and not to a failure of the downward growth of that septum. In these cases fusion of the endocardial cushions occurs in the auricular canal, but even there it is not complete or normal, as shown by the cleft valve segments. If the endocardial cushions are further arrested in their growth the segments are not only cleft, but completely divided with a smaller (Abbott's cases) or larger (our case) defect of the base of the interventricular septum. The plausibility of this explanation is strongly supported by Mall's observations and it has the practical advantage of explaining the defects observed in our case on the basis of a single primary growth deficiency of one structure (the endocardial cushions) rather than by the coincidental failure of two or more structures. However, it should be admitted in passing that defects of the base of the interventricular septum do occur without the slightest evidence of faulty development of the endocardial cushions. Since, as stated above, the processes of fusion and growth of the bulbar and interventricular septa take part in the closure of the interventricular foramen, these defects, as is generally accepted, are due to a deficiency in the septum

and belong in a different category from the defect associated with a persistent ostium primum and a common auriculoventricular orifice.

The frequency of congenital heart disease in Mongolian idiots is well recognized, Cassel [9] finding it in eight of sixty cases and von Hofe [10] in fourteen of one hundred and fifty cases. Abbott,[8] reporting the case of persistent ostium primum referred to above, emphasizes this fact and states that in her experience the cardiac defect not infrequently is a persistent ostium primum. Of the nine cases of persistent ostium atrioventriculare commune with septal defects, which we have found in the literature, four have ocurred in Mongolian idiots — both of Gunn and Dieckmann's cases,[1] one of the six which they cited from the literature, and the one reported by Mönckeberg.[3] With our cases added, five of the ten reported cases have occurred in Mongolian idiots.

Summary

1. A case is reported in which a persistent ostium atrioventriculare commune is associated with a defect in the base of the interventricular septum and a persistent ostium primum. This occurred in the heart of a Mongolian idiot who showed also complete absence of true ovarian tissue.

2. The cardiac defect is believed to be due to faulty development of the endocardial cushions.

3. Four of the nine similar cases found reported in the literature occurred in Mongolian idiots.

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DESCRIPTION OF PLATES

PLATE 44

FIG. 1. The auricles have been partly cut away and the defective interauricular septum reflected exposing the common auriculoventricular orifice with its five valve segments. The two large mesial segments are clearly seen, the anterior above and the posterior below. The right halves of these two segments represent the septal segment of the tricuspid valve, the left halves the aortic segment of the mitral valve. To the right two small segments represent the anterior and posterior tricuspid segments. To the left a single posterior segment is present, the normal posterior mitral segment.

FIG. 2. The right auricle and ventricle are laid open. A large defect of the lower portion of the interauricular septum (persistent ostium primum) is present with the free margin of the septum arching over it. Below this defect the right halves of the mesial segments of the valve guarding the common auriculoventricular orifice are seen (*cf.* Fig. 1). Between these segments there is a deep notch representing the defect in the base of the interventricular septum. The fossa ovale is present in the upper portion of the interauricular septum. The wall of the right ventricle is greatly hypertrophied.

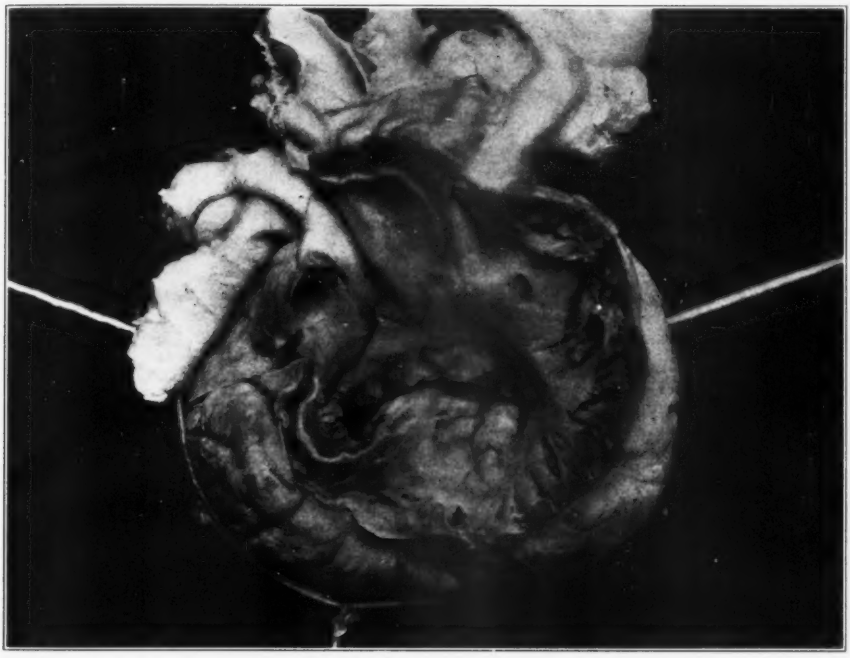

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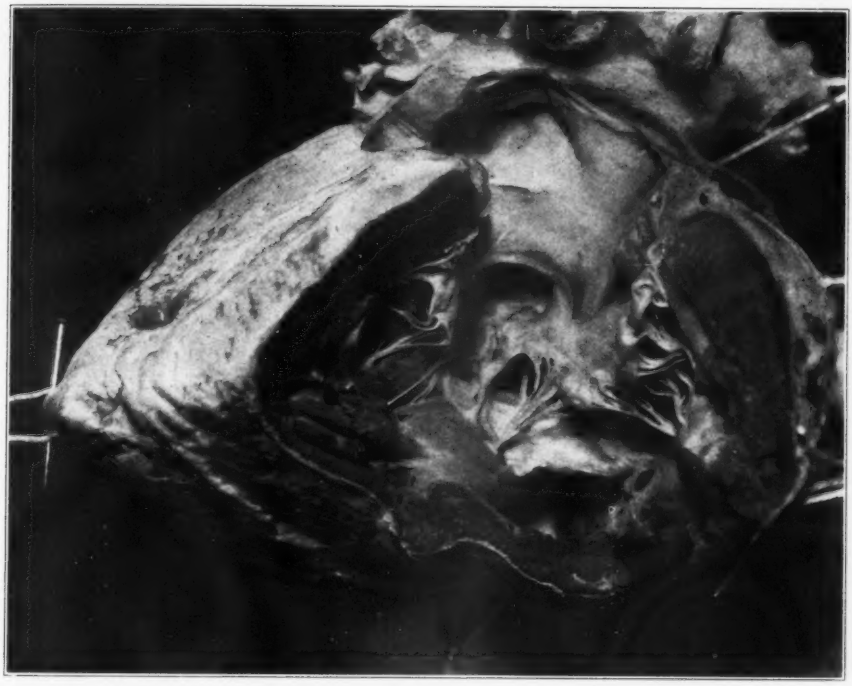
PLATE 45

FIG. 3. The right auricle and ventricle are laid open. The defect of the lower portion of interauricular septum and of the base of the interventricular septum are shown with the anterior mesial segment of the auriculoventricular valve extending through this opening (the left-hand portion in shadow). The endocardium of the interventricular septum near the anterior margin of the defect and of the posterior wall of the conus is much thickened, having a white hyaline appearance. From this region spring a number of chordae tendineae which are attached to the anterior mesial segment and to the anterior tricuspid segment (*cf.* Fig. 1). Some of these chordae are seen extending into the left heart through the defect. Just below the area of thickened endocardium the roomy, thick-walled conus is seen.

FIG. 4. The aorta and left ventricle have been laid open. The aorta is normal. Below its orifice the defect of the base of the interventricular septum is seen. From the free margin of the septal defect arises one large branched chorda tendinea which is attached to the anterior mesial segment (*cf.* Fig. 1).



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THE SPECIFIC CHARACTER OF TOXIC CIRRHOSIS AS OBSERVED IN CINCHOPHEN POISONING *

A Review of Five Fatal Cases

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Cinchophen (phenylquinolincarboxylic acid) was introduced to medicine in 1908 by Nicolaier and Dohrn,[1] and marketed under the trade name of "atophan" (tophi remover). It was originally intended as an eliminant of uric acid in the treatment of gout. Subsequently, because of the similarity of its action to that of the salicylates, it was widely recommended for relief of pain in the various rheumatoid affections. It has formed the basis of many of the well known "rheumatism cures," some of which are so labelled that the name gives no indication that they contain derivatives of cinchophen. Unfortunately, knowledge of its toxic properties did not appear until its use had become general.

Von Müller,[2] Phillips,[3] and Herrick,[4] in 1913 reported that in the course of administration of cinchophen, signs of toxicity became manifest in certain persons. They described the reaction as an urticarial or scarlatiniform rash. Schroeder [5] in 1922, although emphasizing the therapeutic value of the drug in the treatment of gout, indicated its liability to induce toxic manifestations. His cases were illustrative of rather mild poisoning and presented symptoms of headache, gastro-intestinal disturbances and transient jaundice. Worster-Drought [6] in 1923 reported a case of more severe intoxication, but with recovery, and stated that in addition to the symptoms mentioned by Schroeder, jaundice should definitely be added. In 1925 R. C. Cabot [7] reported the death, from acute yellow atrophy of the liver, of a patient who had taken "Weldona" tablets. Concerning "Weldona," the *Journal of the American Medical Association*, for October 1, 1927 contained the following: "the advertising agency

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handling the advertising gave what purported to be a list of ingredients of Weldona, although no quantities were given. The list was: Neocinchophen, Extract of Cimicifuga, Fluid Extract of Phytolacca, Magnesium Carbonate, Light and Powdered Extract of Cascara Sagrada." "A commercial laboratory that analyzed Weldona in September, 1927 . . . did not satisfactorily prove the presence or absence of neocinchophen, but did report that tests for alkaloids showed none present." In Cabot's case the liver appeared to be severely involved in an atrophic process which was recognized as acute atrophy or acute hepatitis. There was associated ascites, with collection of 2500 cc. of fluid, and esophageal varices were also found. Cases similar to these have now been reported by several investigators. Thus Rabinowitz,[8] in 1930 was able to review fifty cases with twenty-five deaths, twenty of which were followed by autopsy. Since Rabinowitz' review, Parsons and Harding [9] have published complete protocols of four fatal cases. The evidence at autopsy in every case thus far reported points to the liver as being the principal site of pathological change, so that the fatal toxic manifestations from cinchophen, in the liver, seem established beyond coincidental relationship.

Five cases of fatal toxicity from the use of preparations of cinchophen have been seen at The Mayo Clinic. These cases lend added confirmation to those previously reported, indicating that the toxic manifestation of cinchophen is principally exerted on the liver, that the lesion produced is essentially destruction of hepatic parenchyma, and that the process is pathogenetically related to toxic cirrhosis. In these cases the preparations of cinchophen had been either self-administered or taken without adequate medical supervision. The patients came to The Mayo Clinic to seek relief from jaundice and related physical disturbances.

Nature of the Toxin

Certain persons possess apparent immunity to the use of cinchophen and others are clearly hypersusceptible. Hench and Rowntree [10] saw a patient who had taken cinchophen in large amounts over a period of eighteen years without the slightest discomfort or disability. One of Reichle's [11] patients had taken 458 gm. of the drug over a period of three years before showing definite evidence

of toxicity. On the other hand, Kessel's [12] patient showed toxic effect with 4.5 gm., and Evans' [13] patient required only about 1 gm. before toxicity became apparent. Worster-Drought's patient had taken 270 grains (18 gm.) in twelve days when an urticarial rash appeared. Taking of the drug was discontinued. After an interval of three weeks it was thought safe to resume the medication; after the first dose, of 7.5 grains (0.48 gm.), more severe toxic manifestations with jaundice appeared. In most instances signs of toxicity have appeared only after use of a considerable quantity of the drug over a relatively long period, or they have become manifest after treatment has been completed, as in the fatal case reported by Willcox,[14] and in one of Loewenthal, Mackay and Lowe's [15] cases in which jaundice appeared two weeks after medication had been stopped. Immediate reactions have been recorded with minimal amounts of the drug following its intravenous use, as in the cases of Kingreen,[16] Hitzenberger,[17] Schwarz,[18] Singer,[19] and Haudek [20] in which diiodo-atophan (biloptin), because of its high content of iodine and its excretion through the liver, was administered in the course of diagnostic cholecystography. Most of the fatalities have developed when administration of the drug was without proper medical supervision, but Willcox and Loewenthal exercised every known precaution in their cases, in spite of which toxicity was encountered.

In cases seen at The Mayo Clinic, because of the manner in which the drug was taken, exact knowledge of the amount used could not be obtained. In one case previously reported by McVicar and Weir [21] (our Case 4), the patient had taken an undetermined amount of atophan for about one year before definite signs of toxicity appeared. In another case reported by Stacy and Vanzant [22] (our Case 2), the patient had taken from one to three tablets of cinchophen for three weeks before realizing that the drug was toxic for her. In another case (Case 1), not reported previously, the patient had taken about twenty-five tablets of cinchophen for only five weeks, according to his story, when a fulminating illness appeared which ended fatally after twelve days of jaundice. Evidently a relatively small amount of drug was taken over a short period of time, yet it was the most fulminating of any of our cases. In two other cases hitherto not reported, the cinchophen was used in the form of oxyliodide. In one of these (Case 3), the patient had taken the drug over

a period of five months, in four courses, each time with early developing evidences of toxicity, such as pruritus and anorexia, until finally, persistence in its use induced grave icterus from which the patient died after four weeks of illness. In the other case (Case 5) of toxicity from oxyliodide a similar story was elicited. This patient rather unwillingly admitted the use of the drug, but evidence was adduced indicating its use for about two weeks. At the end of that time jaundice had appeared. When he ceased to use the drug he improved, only subsequently to resort to its use; toxicity returned and death resulted about five months following the first toxic manifestation.

Some have thought that the variable toxicity is a manifestation of impurity of the drug. Willcox suggested that the toxic principle was the quinolin nucleus, common to all preparations of cinchophen. He advanced his argument by analogy of arsenical compounds; the preparations of arseno-benzol have much greater toxicity for the liver than either inorganic or aliphatic compounds of arsenic. The increased toxicity of the arseno-benzol group, he thought, was due to the benzene nucleus. Since the quinoline nucleus consists of a benzene and a pyridine ring which can yield the toxic ring of free benzene, he suggested this derivative as the actual toxic principle. Sutton [23] advanced the hypothesis that the toxicity was due to the oxidation of the quinoline nucleus into highly toxic nitrocompounds; this would explain the variability in toxicity by the proportionate oxidative disintegration of the original preparation. Rabinowitz took cognizance of the facts that have been given here, but in addition emphasized that the predisposition may rest in the constitution of the patient, as influenced by previous hepatic disease, malnutrition, or any condition which favors decreased storage of glycogen in the liver. From experimental evidence adduced from the use of other toxins which specifically affect the liver, Opie and Alford,[24] Simonds,[25] Graham,[26] Davis and Whipple,[27] and others have indicated that, to some extent, glycogen affords definite protection to the liver, both in its ability to offset toxic destruction of hepatic cells and in its ability to influence the regenerative capacity of the liver following injury.

Review of Five Fatal Cases

Case 1. A man, aged 37 years, had taken cinchophen (about twenty-five tablets) for arthritis over a period of five weeks before he came to the clinic. He suddenly became ill with fever, chills, nausea, vomiting and weakness. The fever disappeared and jaundice developed. Weakness rapidly progressed to exhaustion, stupor supervened and he died in coma twelve days following the onset of the illness.

At autopsy the liver weighed 1320 gm. The color was reddish brown, and the organ was mottled with small areas of ochre yellow. The capsule was slightly wrinkled. The liver was soft and flabby. The cut surface presented mottling of red and yellow. In the yellow areas, indistinct lobular markings were visible.

Microscopically a picture of nearly complete lobular disorganization was presented. Lobular units existed with a small amount of hepatic parenchyma present about the interlobular connective tissue or extending into the lobule up to two-thirds of the distance from the periphery to the central vein. In some lobules only the framework was preserved, for complete parenchymal dismantling of the lobule had occurred. The cellular detritus of the disintegrated hepatic tissue had been entirely cleared away. The initial toxic influence apparently had been directed against the hepatic parenchyma solely, with cellular necrosis and lysis of the cellular remains. The connective tissue, vascular apparatus, and biliary ducts apparently had not been involved in this process, for they persisted without observable reaction. The skeletons of lobules were easily identified by their intact interlobular zones, their sinusoids and central veins. Congestion existed in the bare sinusoidal areas. Frequently congested sinusoids appeared as bands extending between preserved units of parenchyma and connecting the portal and intralobular veins, or extending between two adjacent intralobular veins. Compared with the normal condition these sinusoidal structures were collapsed, but they still constituted the main means of transport of the sinusoidal circulation. The sinusoids about preserved hepatic cords contained but little blood. For the most part the cytoplasm of the hepatic cells was poorly stained; it appeared to be finely granular, with vesicular nuclei containing chromatin in finely divided particles. Completely intact cords were rarely seen. Isolated islands and portions of cords were the rule. Where only an eccentric rim of hepatic parenchyma existed the hepatic cords were atrophic and resembled bile ducts, the so-called pseudotubuli. Where these structures were cut in longitudinal section they appeared as swollen

hepatic cords with rounded terminal ends pointing toward the central vein. These structures were surrounded by collapsed sinusoids and their supporting reticulum. Some of these tubular structures were branched, of irregular size and shape, and appeared to blend in some instances with formation which closely resembled biliary ducts, but which still lay in the intralobular zones. Transitional stages existed from field to field, indicating that the pseudotubuli were remains of disassociated hepatic cords. In support of the morphological evidence of the hepatic derivation of these tubules was the fact that the cells contained lipoids. Interlobular biliary ducts did not contain fat. Only a slight amount of fat was present in the disorganized hepatic cords, except in those in a peripheral situation such as the tubules just described. Further evidence of their hepatic function was shown by the occasional presence of biliary thrombi in them. Proliferation of interlobular biliary ducts was not seen. They were more prominent because of the destruction of surrounding hepatic parenchyma. At the borders of the interlobular zones some tubular structures were observed which had the appearance of biliary ducts, in addition to the previously described tubules. These appeared to represent the terminations of intralobular biliary ducts. Little evidence of regeneration of hepatic cells existed, recovery from the initial injury apparently not having been completely made, but a few clusters of apparently newly formed hepatic cords appeared, always lying near the interlobular structures. These were exhibited as widened hepatic cords containing enlarged hepatic cells with narrow sinusoids between the cords; thus an apparent compensatory hypertrophy-hyperplasia of well preserved, persisting hepatic units resulted. Mitotic figures were rarely found. Leukocytic infiltration was sparse; a few cells of mononuclear and polymorphonuclear types appeared to invade the interlobular connective tissue and bare sinusoidal portions. Connective tissue did not anywhere appear to be newly formed.

Comment: The diagnosis was atrophy of the liver induced by cinchophen, an early stage of toxic cirrhosis. The hepatic changes appeared to be further advanced than the history would indicate. This appearance may be deceptive; one inclines to the view that the changes are far advanced on account of the predominance of connective tissue; however, its presence may be correctly interpreted as only the survival of stromal and vascular structures uninvolved

in the initial hepatic reaction. Repair was held in abeyance by persisting toxic effect or other factors unfavorable to the growth of hepatic cells.

CASE 2. The clinical features of this case were reported by Stacy and Vanzant. The patient was a woman, aged 52 years, with a history of carcinoma of the uterine cervix that had been treated with radium. Pain developed from metastatic carcinoma which involved the right sciatic nerve, for relief of which she took cinchophen. The drug had been taken for about six weeks, one to three tablets daily, when evidence of toxicity appeared. Death occurred sixteen days after the development of jaundice.

At autopsy the liver weighed 903 gm. Its color was red, with yellow, granular, slightly elevated mottling showing through the wrinkled capsule. The organ was soft, and flabby. The cut surface presented similar areas of red and yellow mottling; the yellow areas apparently more clearly demarcated hepatic lobules.

The nature of the initial hepatic lesion was best indicated by the microscopic appearance of the liver in this case. The process was directed against the hepatic parenchyma almost solely, without involvement of the reticulum, vascular apparatus or bile ducts. The toxic effect on the liver resulted in necrosis of the hepatic parenchyma, without evidence of exudative inflammatory reaction. The severity of the initial reaction apparently determined the extent of necrosis, and likewise the capacity of the liver to recover. In this case, a completely unaffected lobule never was found, and in most instances the entire parenchyma of given lobules was destroyed. It was difficult, for this reason, to state that the initial necrosis was central, peripheral, or intermediate in position. Wherever preserved hepatic cells existed, they appeared to be in close connection with the afferent blood supply, a fact which indicated that at least the beginning necrosis was probably not in the periphery of the lobule. The morphological evidence of necrosis was shown by the granular cytoplasm of the cells which took the eosin stain, so that they appeared as ghost forms, usually with complete absence of the nuclei, or with nuclei in a state of karyolysis. In the eccentrically placed, partially preserved units, evidences of degenerative cellular reaction existed, but with some indication that recovery of these cells might have occurred if the patient had survived. The cytoplasm of these cells was likewise pale, took the eosin stain, and was vacuolated, but the nuclei showed little degenerative effect. With scharlach R these vacuoles stained red, but in the necrotic portions there were scarcely

any lipoids in the cells. In the partially preserved cells, fine, yellow granules of bilirubin were also seen. From some of the lobules complete disappearance of the cells had taken place, apparently by lysis. Where this process had taken place the hepatic reticulum and sinusoids persisted and were unchanged. When the lobule became completely devoid of hepatic cells, shrinkage occurred to about half the original size, but where the autolytic process had just been completed, the space occupied by the former hepatic trabeculum could still be seen. Later the space collapsed; the lobular portion was thus decreased in size. In the regions which were devoid of hepatic parenchyma, sinusoids were congested. Microscopic studies disclosed that the grossly red areas represented the skeleton lobules with congested sinusoids, and the grossly yellow portions were from the persisting or necrotic hepatic parenchyma.

Comment: This case exhibits clearly the early stage of hepatic necrosis and cytolysis resulting from intoxication by cinchophen. Cellular detritus was still largely persisting.

CASE 3. A woman, aged 57 years, had taken oxyliodide for rheumatism at intervals for five months. The drug had been taken in three short series, always with the appearance of toxic manifestations such as pruritus and loss of appetite. Finally the fourth trial was persisted in, even though evidence of toxicity reappeared as before. Jaundice finally developed and persisted. Vomiting, weakness, mental lethargy, and finally coma supervened, with death twenty-nine days after the onset of jaundice.

At autopsy the liver weighed 640 gm. It was reddish brown and was mottled by small, slightly raised, yellow granules which showed through the wrinkled capsule. The organ was leathery and somewhat flabby. The cut surface was reddish brown, and small dark green to pale yellow, indistinct, lobular mottled markings were distributed throughout all lobes.

Microscopically the retrogressive features were seen distinctly to be at an end, except for tiny foci of fresh necrosis which existed in some intact parenchymal units. Detritus of the former cytolytic action had entirely cleared. The persisting parenchyma was in the form of units of irregular shape and size, without regard to anatomical lobular demarcation. In some part of their periphery, these units were connected with the interlobular vascular and biliary apparatus, but rarely, if ever, were the central venous regions completely encircled by parenchyma. Central portions of lobules were frequently of triangular shape, due to compression of the bare sinusoidal structures by eccentric ingrowths of hepatic cords, beginning from three separate interlobular zones and crowding the region of

the intralobular vein before the growth. From the central position, bands of congested sinusoids sometimes extended so as to split a lobule between two adjacent intralobular veins, or between the central and portal veins. Evidence existed here, as in Case 1, that most of the sinusoidal circulation passed through these portions, rather than through the narrow capillaries between hepatic trabeculae. These parenchymal units of incompletely restituted lobules evidently were the beginnings of the hyperplastic nodules seen in the later stages. The cytoplasm of the hepatic cells was poorly stained, somewhat hyaline, granular and contained yellowish green granules of bilirubin. Bile thrombi were numerous in the bile canaliculi; sometimes the thrombi were so large that pseudoductal structures were formed by compression of the hepatic cords around the inspissated bile. The nuclei of hepatic cells were pale or vesicular, with finely divided chromatin. In some cells two nuclei were seen, but they were never in a state of mitosis. In the zones of complete parenchymal dissociation (the grossly red portions) there were clusters of eccentrically placed tubules. The appearance here more closely resembled that of bile ducts than in cases previously described. These tubules were not necessarily in relation to interlobular bile ducts but were found extending about the periphery of the lobule wherever normal trabeculae were lost. Variations in form, sometimes resembling hepatic cells and sometimes bile ducts, were evident in them. Many of them contained bile thrombi. There was but little evidence of lipoids in any of the hepatic cells. Lipoid was sometimes stained by scharlach R in the bare, sinusoidal portions where it either lay free, or in the endothelial cells. The connective tissue, as in earlier cases, consisted of persisting former hepatic framework, more contracted and apparently with some new cells derived especially from the sinusoidal endothelium. A faint pink reaction to the Van Gieson stain was for the first time evident in it. Leukocytic infiltration was no more prominent than in cases previously described.

Comment: This case represents maximal hepatic atrophy from intoxication by cinchophen, and illustrates an intermediate stage in the evolution of toxic cirrhosis.

CASE 4. Clinical features of this case have been reported by McVicar and Weir. A woman, aged 37 years, following the birth of a child had experienced general disability with rather vague aches and pains. In the course of pregnancy

she had had complicating toxic hyperemesis. For the postpartum debility and pains she took freely of various analgesics, chiefly amidopyrine (pyramidon) and atophan. Jaundice and mild gastro-intestinal symptoms became manifest after about one year of this indiscriminate usage of drugs and finally manifested itself as icterus gravis. She died about fifteen and a half weeks after the onset of jaundice.

At autopsy the liver weighed 1045 gm. The color was yellowish green with depressed streaks and patches of brownish red. The capsule was smooth, but slightly wrinkled. The organ was firm, leathery, but somewhat flabby. The cut surface was mottled red and yellow. The red was accentuated in the left lobe. Lobular markings existed only in the yellowish portions and were of irregular size and shape. There was edema of the legs, and ascites with 2000 cc. of fluid.

Microscopic examination revealed considerable parenchyma. Often completely preserved or newly formed lobular structures existed. In general, however, the picture presented was one of dissociation with marked irregularity in the size and shape of the parenchymal groups. Frequently bands of fairly vascular connective tissue (the bare sinusoids) were placed between lobules, or extended through the centers of the lobules, dividing them into two or more apparently independent structures. Sometimes the preserved parenchyma was only in the form of a group of hepatic cells, with considerable separation of individual trabeculae by compressed sinusoids or their connective tissue basement membranes. Central veins were more frequently bare than were the portal veins. The regions that were almost completely devoid of hepatic parenchyma and also those that exhibited parenchymal atrophy about the portal structures gave evidence of the presence of peripherally placed tubules in intralobular position. These tubules sometimes completely surrounded the lobule and in their atrophic and compressed state appeared as bile ducts, having but slight resemblance to hepatic cords. The hepatic cells possessed pale, faintly granular cytoplasm containing granules of bile pigment. The cells contained very little lipoid. There was very slight lymphocytic infiltration in the portal connective tissue or in the connective tissue of the bare lobules.

Comment: This was a late stage of atrophy, exhibiting characteristics of early cirrhosis, and unmistakably pathogenetically related to the cases of shorter duration, previously described. Regeneration was not clearly evident. The ascites illustrated that it may occur even in the early cases of cirrhosis, its formation indicating portal

obstruction through contracture and shrinkage of intralobular sinusoids.

CASE 5. A man, aged 62 years, had taken oxyliodide for relief of arthritic pain. Toxicity soon became manifest as anorexia, weakness and loss of weight, and after two weeks jaundice developed. It cleared when taking of the drug was stopped, only to recur with persistence in its use. Finally grave icterus supervened in which the patient died about five months after the initial onset of jaundice.

The liver weighed 1134 gm. The color was brownish red, mottled by yellow, slightly elevated nodular areas varying from 1 to 5 mm. in diameter. The organ was firm and leather-like. The capsule was wrinkled. The cut surface had a mottled red and yellow appearance like that described for the capsule. There was ascites with 2000 cc. of fluid. (See Fig. 1.)

Microscopically the disorganized state of the liver was apparent, but former detritus of the regressive phase had cleared away, and the hepatic parenchyma appeared as revitalized. Well formed parenchymal nodules were found composed of large hepatic cells in widened trabeculae clustered together and either surrounding, or lying adjacent to, the interlobular portal units. Central veins were mostly bare, or they were approached by hepatic tissue on one side, appearing as if peripherally placed with regard to the hepatic unit, but in reality the veins were displaced to the periphery of the former lobule by compression from the hypertrophic hepatic nodules. In the hepatic lobules still existing as skeletonized structures, the peripherally placed rim of tubules was seen as in other cases. The same structures were evident about portal spaces where partial lobular denudation had occurred. These had quite a distinct appearance of abbreviated hepatic cords with cells in a hypertrophic state, as in the nodules of parenchyma. Their bile canaliculi were often shown by the presence of bile thrombi and they contained lipoids as frequently, in fact, as the undoubted hepatic cells contained them. In some places a point of union between these miniature hepatic cylinders and intralobular connecting bile ducts was seen. It was thus possible to see that the two structures were abruptly dissimilar. Gradual transition from one to the other did not exist. At once, as the eye travelled from the hepatic cylinders to the intralobular bile ducts, the cells became low cuboidal with rounded, large, basally placed nuclei. In some places the tubules possessed morphological similarity to bile ducts, especially when they appeared atrophic or when their canaliculi were filled by bile

so as to compress the surrounding cells. The connective tissue was light pink by Van Gieson staining. It gave evidence of considerable contracture and irregular compression, but still could be identified as of former hepatic derivation. There seemed to be some proliferative activity in the endothelial cells, slight in comparison with the amount of connective tissue present. There were a few leukocytes of mononuclear and polymorphonuclear types infiltrating the connective tissue, as in previous cases.

Comment: Early toxic cirrhosis is manifested in this case, with regenerative nodules in beginning formation. Nodules appeared as hypertrophic clusters of hepatic cells from previously preserved intact units. The abbreviated, peripherally placed tubules (hepatic cylinders) had been subjected to the same hypertrophic influences and appeared active rather than regressive. Their morphology more closely approached that of the hepatic cell than that of the cells of the bile ducts, and further, they appeared to have well defined hepatic function in metabolism of fat, and excretion of bile. The connective tissue was but slightly newly formed. It was still possible to determine the framework and sinusoids of the former lobules. The development of ascites indicated the degree of intralobular sinusoidal shrinkage, resulting in portal obstruction.

Discussion

The pathological changes produced by the toxicity of cinchophen, as shown in our cases and in those previously reported by others, are most clearly manifested in the liver. Other lesions, such as fatty changes in the heart and kidneys, mild fat necrosis of the pancreas, and mucosal and serosal hemorrhages were seen, but by comparison they were insignificant. These associated lesions were probably not primarily induced by cinchophen but were secondary to the toxic disturbances concomitant with the atrophy of the liver.

These cases further demonstrate that the hepatic lesion closely, if not exactly, duplicates the picture of acute and subacute atrophy or toxic cirrhosis of the liver, as produced by other causes. The exact picture is apparently determined by the severity and completeness of the initial reaction which either terminates in early death from rapid atrophy of the liver, or is prolonged into definite cirrhosis. From clinical deductions it is evident that less than fatal reactions

may exist which end in recovery, but whether the restoration to clinical normality signifies complete anatomical and functional restoration or restoration in subclinical cirrhosis, can be judged only by future observation in these cases as the patients eventually may succumb from this or other causes. Since the so-called catarrhal types of jaundice are probably on the basis of mild intrahepatic toxic disturbances, some indication already exists that complete restitution, both anatomically and functionally, may occur. On the other hand, Eppinger [28] has shown by biopsy that from catarrhal icterus there may be progression to cirrhosis. This fact also coincides with the well known clinical problem met with in the idiopathic or genuine types of atrophy of the liver; they may appear to pursue a course characteristic of simple jaundice, only to exhibit an unlooked for termination in icterus gravis, and at autopsy the characteristic anatomical picture of subacute atrophy or toxic cirrhosis may be seen.

Marchand [29] in 1895 was probably the first to point out that in the idiopathic types of atrophy of the liver a relatively slowly progressive illness might ensue, terminating months rather than days or weeks subsequent to the onset, and showing in place of the lesion typical of acute atrophy of the liver one in which large nodules of hyperplastic parenchyma alternated with regions of red atrophy. He indicated that this lesion represented multiple nodular hyperplasia, on the basis of initial acute atrophy of the liver, and he set forth further that the resultant lesion was a type of cirrhosis. Mallory [30] in 1911 showed the pathogenetic relationship between acute atrophy of the liver and a specific type of cirrhosis, to which he gave the designation "toxic cirrhosis." He included this in his study as one of the five ways by which cirrhosis might arise. Similar conclusions have been reached by many other investigators.

The persistent concept of the inflammatory nature of all cirrhotic lesions of the liver, implying overgrowth of connective tissue, with compression of the regenerated lobules into nodular formations, has detracted considerably from clear understanding of the initial lesion and its subsequent development into toxic cirrhosis. As far as toxic cirrhosis is concerned, inflammation, excepting in the restricted sense of reaction to injury, is neither the cause nor the outstanding characteristic of the lesion. The reaction to the toxic substance in the early retrogressive period is in the form of fairly specific degener-

ation and necrosis of hepatic parenchyma, with subsequent clearing of the detritus by autolysis and by the phagocytic action of leukocytes attracted into the field by the necrobiotic cells. The necrosis apparently develops and clears without injury to the blood vessels, connective tissue or bile ducts. Since the connective tissue survives this toxic insult without injury, it subsequently does not react to form new connective tissue, and thus the part it plays in the evolution of toxic cirrhosis is only passive. The connective tissue which constitutes the reticulum, sinusoidal structures and larger veins, persists and shrinks, an observation which Mallory made in his early descriptions of the lesion and which more recently has been reëmphasized by Herxheimer.[31]

In the pathogenesis of toxic cirrhosis, the outstanding characteristics thus become: (1) relatively rapid necrosis and autolysis of the hepatic parenchyma resulting in atrophy of the liver; (2) relative increase of connective tissue which arises from the parenchymal loss, without injury or proliferative reaction on the part of the connective tissue framework or vascular apparatus of the liver; (3) predicated on the duration of life following the initial atrophy, regeneration will ensue, arising as reformed nodules of hepatic parenchyma from existent parts spared by the initial necrosis. Because of the extensive initial destruction, this regeneration will be extremely irregular and patchy, but nevertheless large nodules may occur.

The series of cases which we have reported adequately fulfills these three pathological characteristics. In the researches of other investigators added proof may be found. The hepatic lesion caused by cinchophen usually has been referred to simply as acute or subacute atrophy. Rabinowitz, however, recognized the similarity between the hepatic lesions produced by cinchophen and those arrived at through the effects of other etiological factors. He indicated that from cinchophen, as from other agents, the resultant lesion depended on the relative amount of atrophy, regeneration, cirrhosis and nodular hyperplasia, and that with longer duration, opportunity for regeneration with cirrhosis and nodular hyperplasia would be given. Reichle referred to the lesion in his cases as toxic cirrhosis. Parsons and Harding concluded from the lesions of the fifteen fatal cases which they had reviewed that acute, subacute, or chronic hepatic degeneration could result. A careful analysis of our cases should be of value in setting forth clearly the essential similarity of the toxic

changes from cinchophen and those produced from other previously noted agents, such as chloroform and unknown toxins which induce the so-called genuine, or idiopathic hepatic atrophy.

The acute, or necrotic phase of the lesion was best illustrated by Case 2. The universality of the necrosis was the outstanding microscopic picture (Fig. 2). A completely intact lobule could not be found in any of the sections examined. The cells appeared to become necrotic without interposition of fatty changes, and from necrosis they appeared to melt away without provoking inflammatory reaction excepting that a few leukocytes invaded the field, probably as an adjunct in clearing up the detritus left behind. In an earlier stage, preceding the necrosis, the cells may have contained more fat. The anatomical starting point of the necrosis was probably central, for the only preserved parts of the lobules existed in close connection with the portal veins and hepatic arteries. In the other cases this initial reaction had apparently come and gone, for evidences of similar necrotic lesions, even in part, could not be observed in them. By comparison of Case 2 with other cases we might presume that necrosis was rapid, progressive to a certain stage, and ended sharply. Detritus was rapidly cleared, leaving disorganized hepatic cords and lobules behind (Fig. 3). Since life was spared longer in these cases, the initial reaction had undoubtedly been less severe. A greater amount of parenchyma was preserved. As in Case 2, however, the preservation was always best illustrated in the eccentric portions of the lobules (Fig. 4).

The second phase of toxic cirrhosis concerns the increase in connective tissue. Changes described for toxic cirrhosis in general were also met with in our observations when applied to the connective tissue phase. When the necrotic cellular detritus had cleared, the sinusoids and their supportive reticulum could be seen unaltered, except for loss of hepatic cords. Even where the entire lobule represented but a skeleton of its former self, all parenchyma having disappeared, the preservation of this sinusoidal architecture was easily identified (Fig. 6). The spaces formerly occupied by the hepatic cords were clearly evident in Case 2. In some regions in the same case, but better shown in other cases, these spaces were collapsed (Fig. 7). Later, sinusoids themselves collapsed through continued shrinkage, until fairly compact lobular units composed of only a few open and congested sinusoids were found. As the greater compact-

ness became more apparent, the regions appeared relatively more cellular. At times, especially in Cases 4 and 5, actual increase in the sinusoidal endothelial cells was thought to have occurred. The evidence of the reticular and sinusoidal character of the connective tissue was best demonstrated by use of impregnations with silver, such as are revealed by the Perdrau method (Fig. 5). Specific connective tissue stains, for the most part, failed to demonstrate fibrous or collagenous connective tissue, except in the interlobular regions, where the old connective tissue of the liver was unaltered. Thus was substantiated, by these special methods of staining, the distinctive, mainly reticular character of the connective tissue. Elastic tissue stains revealed its presence only in the walls of the blood vessels and the capsule. With regeneration of portions of lobules preserved from the initial necrosis, the sinusoids and reticulum became more evidently compressed between growing parenchymal nodules (Fig. 8) or at their rim. Partial separation of the new and old lobules, by such bands, was seen where they frequently extended between central and portal vein, or between central and sublobular vein. Bands of connective tissue formed of original reticulum were thus seen, dividing lobules into sublobular divisions, with the central vein apparently lying at the periphery of the parenchymal unit. The center of the lobule had in reality not been changed, but regrowth of parenchyma was exceeded by contraction of the connective tissue so that the central vein, lying in the banded, condensed reticulum, appeared to be placed eccentric to the lobule. Even in the late cases, when the contraction changes were most evident, most of the sinusoidal circulation seemed to be passing through these bands rather than between the hepatic cords.

If any differences exist between the lesions produced in intoxication by cinchophen, and those of other etiology, it is in the relative retardation of regeneration in the lesions produced by cinchophen. Grossly nodular formations were not observed even in Case 5, of five months' duration. Comparative studies of cases of toxic cirrhosis of unknown etiology (idiopathic) have shown much greater regenerative capacity in cases of the same and of shorter duration. This inhibition may have been the result of persisting toxic effect, or of other factors not yet definitely known. The duration of the lesion may have been more accurately estimated in the known toxic types. If this were true, then the differences were more apparent than real.

As in the other forms of toxic cirrhosis, regeneration here, although limited, was seen to proceed from intact preserved portions of hepatic parenchyma (Figs. 9 and 10) which had escaped disorganization in the initial destructive lesion. The regeneration was through hypertrophy and hyperplasia of the hepatic cells in nodular formations. The cords were thickened, individual cells had enlarged, and often a syncytial arrangement was found in them. Nuclei were frequently double, but mitotic figures were almost never found. About the periphery of the lobules, where intact trabeculae were absent, or adjoining the interlobular connective tissue when atrophy and disappearance of the cords was found in that situation, tubular structures, sometimes resembling bile ducts, and sometimes resembling miniature hepatic cords, were seen. In Case 1 (Fig. 4) the dissociation of the hepatic cords appeared to follow in such a way that every gradation between these apparently newly formed tubules and the old, intact, but injured hepatic cords could be distinguished. In Case 5, the cells of these tubules shared in the hypertrophy and revitalization, previously described as being found in the larger preserved portions of hepatic parenchyma. In spite of this, the cells were still peripherally placed and gave no evidence of progression beyond the stage of tubules.

It is still held by many observers that these peripherally placed structures represent proliferated bile ducts; some even have gone so far as to believe that they constituted the chief units from which hepatic cells regenerated. Herxheimer and Gerlach,[32] and Blum [33] have observed them in a light quite similar to that which we have described; namely, that morphological evidence and intralobular position point to their derivation from retrogressing hepatic cords, even from the first, when retrogressive rather than regenerative changes dominate the picture. Further confirmation of their hepatic derivation existed on functional grounds, for they contained fat, bile pigment, and apparently excreted bile into structures which were like bile canaliculi (Fig. 11). When seen to connect with intralobular-joining bile duct structures, the cellular change was abrupt, never gradually transitional (Fig. 12), indicative of complete dissimilarity of bile duct cells and those of the tubules. With condensation of the connective tissue, they usually underwent atrophy; then they resembled bile ducts much more than hepatic cells, but still were usually distinguishable from bile ducts. They are insignificant in the

rebuilding of hepatic tissue, as revealed in toxic cirrhosis of cinchophen derivation and in other types, for they regress with the advancement of reticular and sinusoidal shrinkage, before they become of functional importance. From them new lobules probably never form. Regeneration proceeds almost entirely from the better preserved hepatic units, as already indicated. Although in our cases of poisoning from cinchophen the regenerated tissue has never attained large nodular formations, in other cases of toxic cirrhosis nodules of irregular size, shape and distribution, arising from a generally atrophic red substance, constitute one of the outstanding characteristics of the lesion (multiple nodular hyperplasia).

The lesions of toxic cirrhosis, in their pathogenesis and in their completed form, are distinctive from those of the ordinary Laennec, alcoholic, or portal cirrhosis. Likewise, the clinical manifestations are distinctive in each. In the toxic types, a relatively more rapid course is pursued from onset to termination. The long incipient period of Laennec cirrhosis, with latency of clinical manifestations, is a distinctive characteristic, not manifest in the toxic types. The usually early appearance of jaundice, remaining quite constantly throughout the duration of the illness, is an almost invariable picture of toxic cirrhosis, whereas, in the ordinary Laennec form, jaundice is either never an accompaniment or usually appears only as a terminal manifestation. Ascites in toxic cirrhosis is a latent complication, but in the Laennec type the clinical onset of illness is frequently dated from its first appearance.

In toxic cirrhosis there is initial severe and relatively rapid destruction of hepatic parenchyma, similar to, but less decisive than that seen in typical acute yellow atrophy of the liver. The duration of life beyond this initial reaction is primarily dependent on the amount of hepatic parenchyma spared, and secondarily it is determined by the capacity of the hepatic cells to regenerate. The duration of life in the presence of severe parenchymal destruction predicates the extent to which actual cirrhosis will be found. The initial atrophy of the hepatic parenchyma in toxic cirrhosis is always complete in local regions, so that only widely scattered groups of lobules may escape. Since significant regeneration may proceed only from the well preserved groups of cells of former hepatic lobules, the extent to which it may occur is limited. The reformed lobules appear in clusters, usually widely separated from other groups by

portions completely devoid of these regenerative forms. In the Laennec form of cirrhosis the initial atrophy is apparently never as severe, and likewise it never occurs so rapidly. Thus, the regenerative nodules are more abundant and uniformly distributed, with less variation in size and shape, more nearly duplicating the former hepatic units. In the toxic types, at least, the connective tissue largely represents the preëxisting hepatic reticulum, sinusoids and interlobular partitions made prominent by the disappearance of the hepatic cords. Proliferative activity never plays a prominent part in this increase of connective tissue. The contracture and shrinkage of this original stromal substance parallels the contracture and hardening of the organ as a whole, augmented in part by the regenerative nodular forms. Later it may assume the characteristics of fibrous or collagenous connective tissue, as Rinehart [34] and others have indicated that from organic reticulum this transformation may take place. Even in the late cases of toxic cirrhosis, in the grossly red portions the skeletal structures of former lobules still persist, an identifying characteristic not seen in other types of cirrhosis. The inability to identify these skeleton lobular structures in Laennec cirrhosis, combined with the associated, almost constant and abundant lymphocytic collections in the evidently increased connective tissues, apparently indicate a difference in the pathogenesis of these two distinctive types of hepatic atrophy. The appearance of the so-called proliferated bile ducts in each type needs further study before a conclusive statement can be made. Apparently, in the toxic type, as we have indicated, their formation is from regressive hepatic trabeculae, and although they usually present progressive atrophy, sometimes they become activated by the same influences which govern the activation to growth of other hepatic cells. Not only, however, is this development hindered by the action of the primary toxic factor, but also by the progressive contracture of stroma which eventually literally crowds them from the picture, for they become contracted to small structures which resemble bile ducts or assume the appearance of mere strands of parallel cells.

Summary

1. Preparations of cinchophen have been shown definitely to be toxic for certain persons. The toxic effects are directed most severely and specifically against the liver.

2. Unknown factors, apparently independent of the quantity of the drug used, appear to be significant in creating a predisposition or idiosyncrasy for the drug.

3. Various grades and stages of hepatic degeneration have been described. These are presumably dependent on the completeness and rapidity of the initial reaction. The reaction may be rapid and complete, with induction of acute atrophy of the liver, or slower and less complete, with apparent recovery. Intermediate between these two extremes subacute forms of intoxication may ensue and may become manifest both clinically and pathologically as a type of hepatic atrophy or cirrhosis, which corresponds in its anatomical characteristics to the distinctive toxic cirrhosis as described by Mallory.

4. The clinical and anatomical characteristics of toxic cirrhosis appear to be specific and essentially dissimilar to the ordinary Laennec or portal type.

5. The clinical data and correlated studies of pathological anatomy in five cases of intoxication from cinchophen constitute the basis for this study.

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DESCRIPTION OF PLATES

PLATE 46

FIG. 1. Case 5. Toxic cirrhosis caused by cinchophen, of five months' duration.

FIG. 2. Case 2. Extreme lobular disorganization and necrosis. Congested sinusoids. The best preserved unit is at the lower left, adjacent to the interlobular circulation (not included). Interlobular structures are at the right, midway between top and bottom; they are surrounded by bile ducts and intralobular sinusoids which are made apparent by parenchymal autolysis; congested central vein is at the upper left, surrounded by prominent sinusoids and reticulum. Hematoxylin and eosin stain. × 65.

FIG. 3. Case 2. Complete dismantling of lobule, with cellular detritus cleared. Some sinusoids and the central vein are congested, other sinusoids with reticulum are collapsed. At the upper left, a portal vein is surrounded by bile ducts made prominent by disappearance of parenchyma. Hematoxylin and eosin stain. × 120.

FIG. 4. Case 1. A less destructive lesion than those of Figs. 2 and 3, with portions of lobular trabeculae, regressive but simulating biliary duct structures. Actual bile ducts are prominent in the interlobular zone, upper left. Hematoxylin and eosin stain. × 150.

FIG. 5. The sinusoidal (intralobular) reticulum of normal liver as revealed by silver impregnation by the method of Perdrau.

FIG. 6. Case 2. The intralobular sinusoidal structures and reticulum as revealed by silver impregnation by the method of Perdrau. Necrotic detritus is still persisting somewhat, but where clearing has occurred sinusoids are collapsed. × 125.

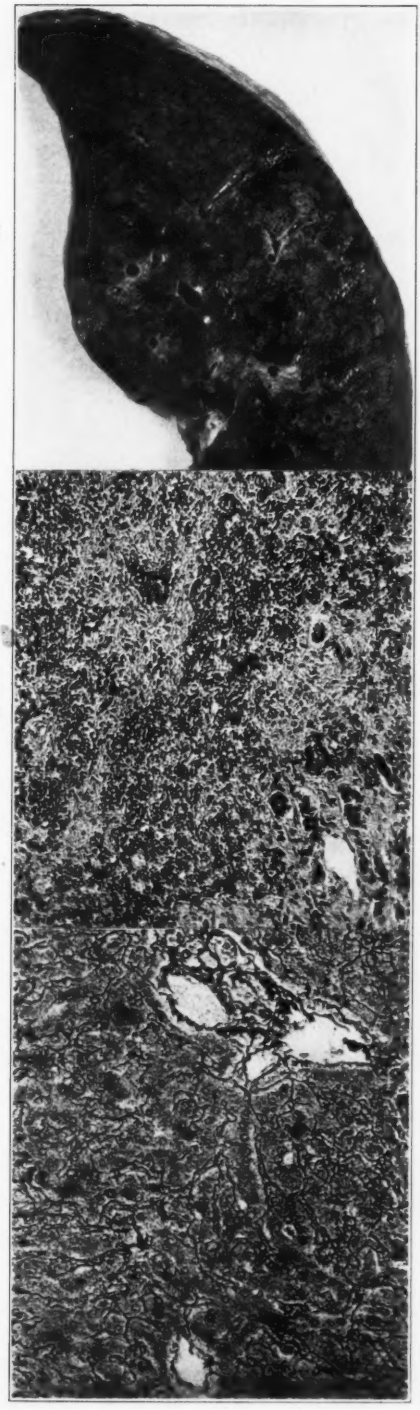

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PLATE 47

FIG. 7. Case 4. Lobular reticulum in late atrophy as shown by silver impregnation, by the method of Perdrau. Lobular landmarks are evident: central vein, collapsed sinusoids, peripheral rim of tubular intralobular structures and interlobular structures, upper left. × 110.

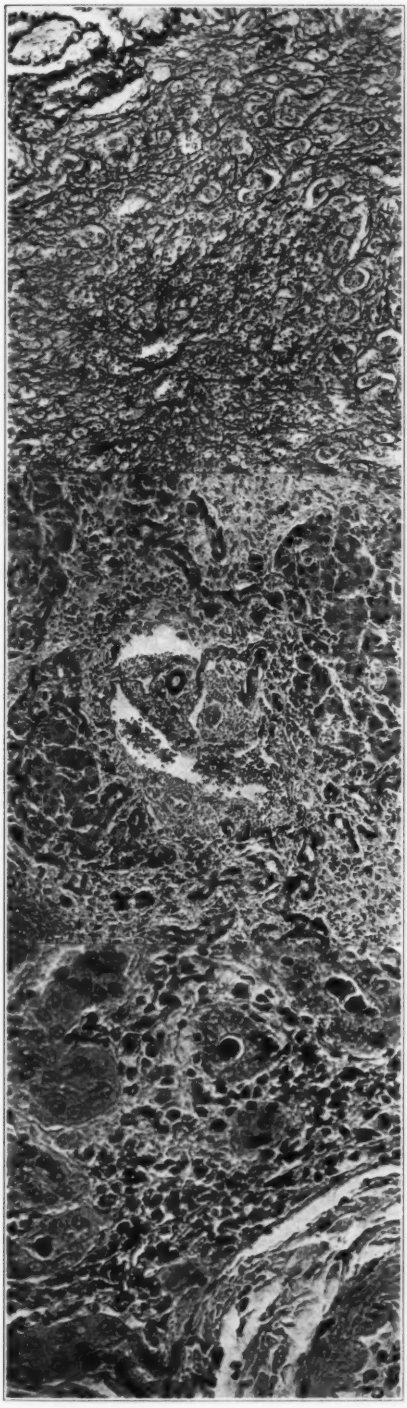
FIG. 8. Case 5. Compression of skeletonized lobule by growing parenchymal nodules as revealed by silver impregnation by the method of Perdrau. A central vein is lying in compressed lobular stroma at the periphery of a regenerated nodule (not included) at the right. × 110.

FIG. 9. Case 3. Units of trabeculae with evidence of recovery from toxic effect, surrounding an interlobular zone, in which bile ducts are prominent. Pseudo-intralobular ductal formations are in the miniature hepatic cords formed by dilatation of bile canaliculi. Nodular regeneration proceeds from such partially preserved lobules as shown here. Hematoxylin and eosin stain. × 100.

FIG. 10. Case 5. Regenerated lobules in nodular formation. A band of hepatic reticulum is compressed between regenerated parenchymal units. Tubular structures consisting of bile ducts and regressive hepatic cords lie in original but contracted hepatic stroma and surround the newly formed lobules. An hepatic vein lies at the periphery of the regenerated lobule. Hematoxylin and eosin stain. × 50.

FIG. 11. Case 5. Tubular structures exhibiting bile thrombi, at the periphery of a lobule. The resemblance to hepatic cells in these structures is striking. Hematoxylin and eosin stain. × 350.

FIG. 12. Case 5. Peripherally placed intralobular tubular structures, showing abrupt transition between the apparent bile duct and the miniature hepatic cord. A characteristic bile canaliculus lies between the cell rows of the miniature hepatic cord. Granules of bile and lipochrome pigment are within the hepatic cells. Hematoxylin and eosin stain. × 300.



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GRANULOMATOUS ABSCESS OF THE LIVER OF PYOGENIC ORIGIN *

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Abscesses of the liver are relatively uncommon in comparison with the high incidence of other intra-abdominal infections. Nevertheless, there is opportunity for infection of the liver because it is in direct vascular communication, through the portal circulation, with most of the abdominal viscera. In addition, opportunity for infection with formation of abscesses is afforded by way of the hepatic artery, the bile ducts and the lymphatic channels. The protection of the liver against infection is to some extent dependent on its abundant blood supply, with free movement of blood through its sinusoidal vascular system. Further inhibition to localization of infection is afforded by the phagocytic reticulo-endothelial cells which line the sinusoids, and other less definite but none the less potent factors of immunity, in the production of which the liver is probably directly concerned.

PATHOGENESIS OF HEPATIC ABSCESSES

Abscesses which originate from infection carried by way of the hepatic artery are almost never found, except in a general pyemic process when the liver, with the other viscera, may suffer from dissemination of infective material. Before hepatic infection can occur from this source, pulmonary or cardiac involvement is almost a prerequisite. Microörganisms of sufficient virulence to infect healthy tissues usually will not pass the lungs without first localizing there, subsequent arterial propagation of the infection coming from the focus thus formed. Hepatic abscesses which originate in this way are multiple, small, and usually involve all lobes of the liver equally. Subcapsular localization is most common. These abscesses have no

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special clinical significance, nor are they of long duration, since the patient dies of the generalized sepsis before attention is directed to the liver. There are instances in which superficial, localized infection appears to be the only source of an abscess of the liver and apparently produces its effect without first involving lungs or heart. Reiniger,[1] Kaufmann,[2] and others explained it on the basis of retrograde embolism and thrombosis of the hepatic veins. Such an occurrence, however, must be extremely rare. Small lesions could exist in the pulmonary parenchyma without detection and no doubt may constitute the focus for arterial dissemination, with localization in the liver.

Abscesses of the liver, which originate in the biliary tract, should be considered with diseases of the gall-bladder and the bile ducts. Ascending infection is not a probability unless obstructive lesions are complications, and then suppurative cholangeitis may lead to formation of hepatic abscesses. Abscesses of this type are identified by their content of bile and their communications with the dilated biliary ducts.

Extension of infection from within the field of drainage of the portal vein is responsible for the greatest number of hepatic abscesses. This extension may occur by embolic masses of bacteria, but more frequently there is preceding local thrombophlebitis produced by the primary lesion, and the hepatic dissemination occurs as a result of detachment of infected thrombi. The original thrombophlebitis may extend to pylephlebitis with invasion of the liver and formation of abscess. The infrequency of localization of infection in the liver indicates that showers of infected embolic thrombi are almost essential predisposing factors in formation of hepatic abscess. Microörganisms unassociated with thrombi probably pass through the liver in most instances without producing suppuration.

The source of the hepatic infection may be apparent to clinical, as well as to pathological examination. These primary sources of hepatic infection are given by Rössle [3] in accordance with their frequency, as follows: colon, appendix, spleen, pancreas, small intestine and stomach. With the exclusion of amebic abscesses the appendix becomes the most common primary focus. In newly born infants infections of the umbilicus may proceed to thrombophlebitis of the umbilical vein, and with extension to the portal vein abscesses of the liver may supervene. Ulcerations of the rectum, or infected internal

hemorrhoidal veins, have been recorded as other sources of portal infection. Rössle described two cases of splenic abscess with secondary hepatic infarction and suppuration. Direct, penetrating trauma to the liver may easily provoke formation of abscess, but more interesting are the observations of Townsend [4] and Jacoby [5] that severe contusions to the liver apparently evoke the local lowering of resistance which allows infection, with formation of abscess, to follow.

In some cases the hepatic suppuration appears to be the primary clinical phenomenon, and no evidence can be found by the pathologist to alter this opinion. Because of the apparent primary character of such abscesses they have been referred to as primary hepatic, idiopathic, or cryptogenic. It is unlikely, however, that the hepatic abscess ever represents primary infection, but more likely that the primary lesion is obscure, usually within the region of the portal drainage, and without subjective or objective signs, thus escaping the attention of both physician and patient. Healing may be so effectually consummated that even by careful examination the pathologist cannot give the needed help in offering a solution after death of the patient. Abscesses of this type have been referred to by Norris and Farley,[6] Lepehne,[7] Ludlow [8] and Williamson.[9]

Abscesses resulting from a source known to be primary in the tissues contributing to the portal circulation are most frequently found in the right lobe of the liver. Sérégé,[10] by means of injections of Chinese ink, seems to have offered an explanation for this. He showed that two currents of blood exist in the portal vein, one originating from the superior mesenteric and pancreatic veins, and passing to the right lobe; the other coming from the inferior mesenteric and splenic veins, and passing to the left lobe. Since the primary foci are most often thought to be in the distribution of the superior mesenteric vein, and if the observations of Sérégé are true, this would seem to explain the greater frequency of involvement of the right lobe.

Most of the so-called idiopathic abscesses have similar right lobar distribution and otherwise partake of the same anatomical characteristics as those of known portal pathogenetic relationship, even to the occasional association of pylephlebitis. These points of similarity suggest, as one would suspect, that their pathogenesis is the same, only our inability to localize the original lesion constituting the difference.

Etiology: A great number of microörganisms have been reported as playing the causal part in hepatic suppuration. My experiences concur with the reported observations of others in emphasizing the prevalence of pyogenic micrococci in this form of suppuration. Staphylococci predominate, with streptococci closely second. Other organisms occasionally constitute the exciting factor, such as members of the genus Clostridium. *Clostridium welchii* has been reported by others and we once found an organism corresponding to *Clostridium oedematis-maligni* (*Vibrion septique*). As a complication to infections with typhoid and paratyphoid organisms, hepatic abscesses have been reported, but their occurrence is rare. Pseudomonas and fusiform bacilli have been found rarely. The association of the actinomyces, streptothrix, blastomyces and entameba are well known. Infections by *Escherichia coli* in the liver, as elsewhere, probably have been overemphasized.

Case Reports

Several abscesses of the liver, having the characteristics of granulomas, have been seen at The Mayo Clinic. These usually have presented an insidious clinical onset, slowly progressing into chronicity without, as a rule, clearly revealing the source of the hepatic infection. Their drainage usually was unsatisfactorily completed because of their multilocular character and their tendency to persist as granulomas, with sometimes formation of sinus tracts. In their insidious progress, chronicity, cryptogenic character and anatomical features they have simulated the granulomas of actinomycosis or tuberculosis. The suspicion that either of these might have been the cause of the condition in these cases could never be confirmed. Bacteriological studies, on the other hand, have shown the constant presence of the pyogenic micrococci, both staphylococci and streptococci exhibiting this association. Thus, we may speak of these abscesses as pyogenic granulomas. The clinical aspects of hepatic abscesses will be presented briefly. Special emphasis will be given here to the duration, source, etiology and pathological anatomy. To illustrate the special characteristics of this disease protocols of eight cases will be presented.

Case 1. A man, 44 years of age, complained of severe pain in the right upper abdominal quadrant, with nausea, chills and fever of three weeks' duration.

Abdominal exploration revealed an enlarged liver. An hepatic abscess was found and drainage was instituted. Death occurred about five weeks from the onset of symptoms.

At autopsy the liver weighed 1948 gm. There were multiple multilocular abscesses which involved only the right lobe. The original hepatic focus was of central situation, with some peripheral extension. There was associated suppurative thrombosis of the portal and splenic veins. A small abscess 3 cm. in diameter was situated in the head of the pancreas and communicated with the thrombosed splenic vein.

Microscopically it could be concluded that the multilocular cavities were comparatively independent in structure because of the encapsulation of each small unit by compressed hepatic parenchyma. Adjacent to the exudate, the hepatic cells gave evidence of hyaline degeneration of the cytoplasm and other stages of retrogression to necrosis. Some fibroblasts were present in the capsule. The exudate was of polymorphonuclear leukocytes and clumps of bacteria were prominent.

Cultures taken from the hepatic abscess revealed *Staphylococcus aureus* and streptococci of a hemolytic type. Gram-Weigert stains of the tissue revealed many Gram-positive cocci in chains and clusters.

Comment: The only focus of infection found was the pancreatic abscess. This, however, could have been secondary to the pylephlebitis. Since this case presents a multilocular abscess (Fig. 1), associated with known thrombopylephlebitis, it supports the theory that these abscesses are of portal embolic origin, whether frank portal thrombosis exists or not.

CASE 2. A man, 47 years of age, entered The Mayo Clinic with an acutely perforated duodenal ulcer and consequent peritonitis. Symptoms of ulcer had been present for twenty years. The perforation was closed but the course of the disease continued to be septic, with irregular fever and progressive weakness. Death occurred about two months after the perforation.

At autopsy the liver weighed 4080 gm. An abscess 15 cm. in diameter existed in the right lobe of the liver, involving the inferior and posterior portion and extending laterally. It contained 1200 cc. of thick, greenish pus, but this was not bile-stained. The abscess was crossed by interlacing trabeculae separating it into several large cavities. The main wall of the cavity consisted of compressed hepatic tissue of grayish color, with some fibrosis. Thrombi were not observed in the portal veins.

Microscopically the outer part of the wall of the abscess consisted of compressed hepatic parenchyma showing varying stages of cellu-

lar degeneration, progressing to necrosis as the region of infection was approached. In this zone thrombosis of the hepatic and portal veins was observed, with purulent infiltration of the thrombi and purulent phlebitis. Within the zone of encapsulating hepatic tissue there was fibrosis, which showed evidence of old and recent hemorrhage, and which was infiltrated with large mononuclear and polymorphonuclear leukocytes. Within this, and adjacent to the field of suppuration there was a zone of hyaline material which took the eosin stain, and into which a scaffolding of fibroblasts was penetrating. The exudate was predominatingly of polymorphonuclear leukocytes, and much necrosis was evident. Colonies of bacteria which resembled actinomyces were present, but with higher magnification these were revealed as staphylococci. The interlacing connective tissue trabeculae formed the partitions seen in the abscess cavities and represented the proliferated hepatic stroma. Bile ducts persisted in these strands.

Staphylococcus aureus was isolated in cultures from the hepatic abscess. Gram-Weigert stains of the preparations of tissue revealed many Gram-positive micrococci.

Comment: This case of chronic hepatic abscess is illustrative of an intermediate stage of progression with incomplete solution of the hepatic substance (Fig. 2), and some features of early granulomatous change. The etiological relationship to the peritoneal infection following perforated duodenal ulcer appears to have been well established.

CASE 3. A boy, 14 years of age, entered The Mayo Clinic complaining of swelling and tenderness of the left cervical region and right cheek. The cervical condition had been present, with alternating periods of healing and suppuration, for about two years. Six weeks prior to his admission, he had become suddenly ill, with dizziness, coryza, non-productive cough, fever, vomiting, and slight jaundice. Study of the suppurative process in the neck failed to give evidence either of tuberculosis or actinomycosis. Blood cultures were negative. He had an irregular fever, with daily fluctuations from 97° to 103° or 105° F. Abdominal exploration revealed an hepatic abscess, and drainage was instituted. Death occurred twenty-seven days after operation and about three months subsequent to symptoms referable to infection of the liver.

An autopsy was performed. The liver weighed 3085 gm. There were multiple multilocular abscesses involving the right lobe of the liver. Smaller ones, formed by peripherally extending infection from the primary hepatic foci, were seen. The largest abscesses were of irregular leaf shape, as described by Kaufmann, and were composed of well defined multicentric foci. Actinomycosis was strongly suggested by their appearance, as well as by the history of cervical suppuration.

There was no pylephlebitis. 2000 cc. of ascitic fluid were found, and there were 700 cc. of fluid in the right side of the thorax. There were multiple embolic abscesses in the right lung.

Microscopically, there were well defined granulomatous encapsulations about each focus of the multilocular abscesses with suppurating centers consisting chiefly of polymorphonuclear leukocytes in which necrosis was evident. Colonies of Gram-positive cocci were abundant in the exudate.

Cultures of the hepatic and cervical abscesses contained *Staphylococcus aureus* and streptococci of a hemolyzing strain. Gram-Weigert preparations of the abscesses of the liver revealed numerous colonies of micrococci. No trace of actinomyces could be found.

Comment: This case represents a typical portal embolic abscess (Fig. 3), in spite of the cervical suppuration preceding it. There was no evidence of a retrograde embolic process in the hepatic veins. The source of the hepatic infection was probably in the portal circulation in spite of our inability to find it at the time of the autopsy. However, it is possible to follow events from cervical suppuration to pulmonary involvement and localization in the region of the portal circulation with secondary hepatic emboli supervening. The chronic suppuration in the neck led further to the suspicion of the presence of tuberculosis or actinomycosis, but confirmatory evidence for this could not be discovered.

CASE 4. A man, 27 years of age, complained of fever and weakness of two months' duration. This started as a sudden pain in the right lower part of the abdomen, and a diagnosis of appendicitis was made by his physician at home. Four days later, fever became marked, and continued with a somewhat irregular course. At laparotomy a subphrenic abscess was drained. Subsequent to the drainage, as before, the temperature continued to be of the characteristic septic type of hepatic suppuration, varying from 97° F. in the morning to 105° F. in the afternoon with frequent chills. He died two weeks subsequent to the drainage, and about three months after the probable onset of the illness.

At autopsy, fibrous adhesions were found extending between the superior surface of the liver and the diaphragm. The liver weighed 2865 gm. On section, in the right lobe just above the hilum, several intercommunicating abscess cavities, some with multilocular architecture, appeared. These extended laterally, and all together involved a region of liver about 10 cm. in diameter. Small, single or multilocular cavities of more recent origin appeared in the peripheral zone, a considerable distance from the old region of involvement. The larger cavities contained thick, purulent exudate. The centers of many of the multilocular regions appeared to be caseous. Thrombosis of the portal vein was not evident. There were associated subphrenic infection and embolic pulmonary

abscesses with empyema. Recent thrombosis of the internal iliac veins, vena cava and right auricle also were found.

Microscopically the small foci of more recent formation gave evidence of their thrombotic nature, for suppurative thrombi were contained in partially intact portal veins. In the most recently formed foci there was no proliferative reaction about the periphery, but those of longer duration and representing the original hepatic foci of infection had walls composed of recently formed granulation tissue. Endothelioid and giant cells also constituted a part of this wall. Farther removed from the field of infection the encapsulating connective tissue was of more fibrous type. The exudate was composed of polymorphonuclear neutrophilic leukocytes combined with many large and small mononuclear cells, and in some fields there was hyaline necrotic substance with very few leukocytes present. Colonies of micrococci were present everywhere in the exudate. Surrounding the larger abscesses the hepatic tissue was compressed with central lobular congestion and necrosis.

Cultures taken from the hepatic abscess contained *Staphylococcus aureus*. Gram-Weigert stains of the tissue revealed clusters of Gram-positive staphylococci.

Comment: The origin of this hepatic infection could not be well established. The tip of the appendix was slightly thickened and infiltrated with lymphocytes, but did not present changes such as should have been found in a quiescent interval after a severe, preceding acute inflammatory process. However, no other explanation was revealed by the postmortem studies.

CASE 5. The patient was a man, 32 years of age. Five years before his registration at the clinic he had undergone appendectomy, and two years after that operation, hemorrhoidectomy. The illness of which he complained had begun with a sudden, constant, severe sacro-iliac pain. Later, intermittent epigastric pain had developed and this had become localized in the lower part of the abdomen. Subsequently pain in the right side of the thorax, jaundice and high fever had developed. Laparotomy revealed an abscess of the liver and drainage was instituted. The patient died about seven weeks after the hepatic drainage, and four months from the inception of the illness.

At autopsy the liver weighed 2500 gm. It was intensely stained with bile. There was no obstruction to the ducts or any cholangeitis. Two multilocular abscess cavities were present in the right lobe, one on the anterior surface and one in the inferior portion. The inferior abscess measured 10 cm., 4 cm., and 3 cm. in various diameters, and the anterior one was 5 cm. in diameter. Surrounding the large abscesses smaller similar lesions were developing. The ab-

scesses were composed of large multilocular cavities with intercommunications. In some places the trabeculae had broken down to tag-like bands that were adherent to the walls. Fibrous encapsulation was evident. There were beginning subphrenic abscess and empyema on the right side. Chronic ulceration was present in the terminal portion of the ileum. There was no evidence of pylephlebitis.

Microscopically the hepatic abscesses appeared to be irregularly outlined and multiple. The encapsulating structure was of fibrous tissue lying on compressed hepatic substance. In the innermost portion of the wall, fibroblasts, blood vessel sprouts and giant cells were evident, and this zone was infiltrated by mononuclear and polymorphonuclear leukocytes. The exudate consisted of polymorphonuclear leukocytes, but in part it was composed of hyaline-like material mixed with cellular detritus. Colonies of bacteria were numerous in the exudate. Considerable necrosis and hemorrhage existed in the hepatic tissue adjacent to the abscesses. The ulcerative lesions of the ileum exhibited chronicity, and there were lymphocytic collections and endothelial proliferation throughout the intestinal wall. The ulcers did not have specific characteristics.

Cultures from the abscess of the liver revealed green-producing streptococci. Gram-positive streptococci were abundant in the tissue.

Comment: The insidious onset and chronicity of this hepatic abscess, together with the prodromal localization of pain in the lumbar and lower abdominal regions, constitute the outstanding characteristics. Williamson has indicated that the pain may be referred to the lumbar region from the diaphragm in subdiaphragmatic or hepatic suppuration. In the early stages of this case, typhoid fever, undulant fever and tularemia were suspected but could not be proved. The hepatic lesions at autopsy suggested actinomycosis, but actinomyces were never found. The probable source of the abscesses of the liver was a cryptogenic intestinal infection, with embolism to the liver. The residual of this may have persisted as ulcerative enteritis. The appendectomy or the hemorrhoidectomy, performed some years before, could be of significance as constituting the primary focus, but the interval of good health following these procedures renders this improbable.

CASE 6. A man, 31 years of age, whose illness began as appendicitis, subsequently had chills, fever, nausea, vomiting and pain in the right side of the thorax. Empyema of the right pleural cavity developed which was drained.

The drainage persisted, and several months later evidence of hepatic suppuration developed. Hepatic drainage was then instituted. Search was repeatedly made in the material which drained from the thorax for actinomyces and *Mycobacterium tuberculosis*, but always without discovery of either. The patient died seventeen days after the liver was drained and ten months from the beginning of the illness.

At autopsy, the liver weighed 2715 gm. In the lateral portion of the right lobe, a spongy, multilocular abscess was found which measured 10 cm. in diameter. The individual abscesses which comprised this mass were not more than 5 mm. in diameter. Each contained thick yellow pus. The trabecular partitions of the abscess appeared as grayish, fibrous encapsulating membranes 1 to 2 mm. in thickness. The peripheral encapsulation of the entire mass did not differ from the honeycomb-like trabeculae, except that compression of the hepatic tissue had occurred at the border. Evidence of old, healed empyema on the right side, and terminal embolic pulmonary abscesses were additional disclosures. There was no pylephlebitis. The distal portion of the appendix was bound down by fibrous adhesions and the lumen was obliterated. There was no evidence of recent inflammation.

Microscopically the encapsulations of the individual units of the large multilocular abscess appeared to be of the same duration. Their structure was of fibrous connective tissue, apparently originating from hepatic tissue, because occasionally atrophic bile ducts could be identified. Nearer to the zone of suppuration young fibroblasts and endothelial cells became the principal framework of the capsule. Here there was infiltration with mononuclear and plasma cells, and polymorphonuclear leukocytes. The periphery of the exudate appeared as a layer of fibrin with few leukocytes, invaded by fibroblasts. The exudate within this was predominatingly of polymorphonuclear leukocytes, but much of it was necrotic. Colonies of bacteria were numerous. The hepatic tissue about the periphery of the multilocular mass gave evidence of compression, fatty and hyaline cytoplasmic changes in the hepatic cells, with considerable atrophy and disarrangement of lobules.

Gram-Weigert stains of tissue revealed numerous colonies of staphylococci in the exudate.

Comment: This case illustrates a multilocular or honeycomb abscess like that seen in actinomycosis, persisting into chronicity without exhibiting even sufficient lytic qualities to break down the divisions of hepatic tissue which originally constituted the encapsulating membranes of the multilocular abscess. Stimulation to granulomatous formation rather than advancement of the suppurative characteristics was the outstanding anatomical feature of the hepatic lesion. The onset followed a questionable attack of appendi-

citis, but attention was never focused on the liver until fully nine months had elapsed. During this time, the progressive chronic empyema, which persisted in draining, seemed to account for all the symptoms. As this cleared, however, the evidence of hepatic suppuration was revealed. Whether the appendix was the primary focus of infection is not clear, but that the abscess was of portal embolic origin seems certain. The empyema was probably secondary to the hepatic involvement, but the thought that the abscess of the liver may have followed the empyema, with involvement of the right hepatic lobe, should at least receive some consideration. The only evidence that the appendix was the primary focus consisted in the finding of an adherent tip, with obliteration of the lumen of the adherent portion.

CASE 7. In April, 1926, a woman, 19 years of age, noted the onset of cough, which persisted with mild attacks of pain in the right hypochondrium. In June, abdominal exploration revealed an abscess in the right lobe of the liver. Drainage was instituted and persisted up to the time of her death. Actinomycosis and tuberculosis were repeatedly excluded by study of the material which drained. As a terminal feature there were multiple subcutaneous abscesses, and osteomyelitis of the right tibia. The patient died in January, 1928, about one year and nine months after symptoms referable to the liver appeared.

At autopsy the liver weighed 1800 gm. A large, multilocular abscess 7 cm. in diameter was found in the right lobe of the liver. The border was sharply demarcated from the surrounding liver, but a heavy fibrous encapsulating membrane was not present. The surrounding hepatic tissue was compressed and congested. The large abscess appeared to be composed of multiple confluent small abscesses, each surrounded by an irregular zone of grayish white, firm substance in which yellowish foci were visible. Small abscesses were found in the lungs, pancreas, spleen, kidneys, ankles, elbows and wrists. There was no evidence of pylephlebitis.

Microscopically the encapsulating membranes of each suppurating focus of the multilocular hepatic abscess were of compact connective tissue in the peripheral part, which changed to a fibroblastic type of tissue toward the zone of suppuration. Here, too, numerous endothelioid cells were crowded together. Giant cells of foreign body and Langhans' type appeared in this zone. The periphery of the exudate was composed of polymorphonuclear leukocytes, but many mononuclear leukocytes were interspersed. Centrally the exudate took the eosin stain and was of acellular, hyaline appearance. Colonies of bacteria were sparse, Gram-Weigert stained sections revealing only a few staphylococci. No actinomyces or *Mycobacterium tuberculosis* were found.

Exudate from the hepatic abscess revealed staphylococci in smears, cultures, and in preparations of fixed tissue. Actinomyces were not found. *Mycobacterium tuberculosis* was not found in smears.

Comment: This case is representative of the so-called idiopathic hepatic abscess. There was an indefinite history of influenza, and the hepatic condition was associated in its beginning with cough and hypochondriac pain. At autopsy the origin of the infection was not found, but from the likeness of the hepatic abscess to those seen in earlier cases, a portal type of distribution of the infection seems most probable. The multiple abscesses of other organs found at autopsy probably represented pyemic dissemination of infection from the old hepatic focus. The long clinical course, with persistence of a draining sinus, suggested actinomycosis. Anatomically the similarity was also marked (Fig. 4).

CASE 8. The illness of a man, 39 years of age, began in February, 1924, with persistent abdominal pain, fever and diarrhea. These severe symptoms were present for three weeks, but the abdominal pain persisted for four months. After it had subsided, weakness, anorexia and occasional attacks of pain continued. The illness continued with alternating periods of well-being and of exacerbation until the patient's death November 5, 1926, about two years and nine months after the first symptoms.

At autopsy the liver weighed 4250 gm. There were dense, fibrous adhesions between the right lobe and the inferior surface of the diaphragm. A fluctuating mass appeared in the right lobe, which on section was shown to be an abscess. It was 12 cm. in diameter and contained about 1000 cc. of thick, greenish yellow pus that was not bile-stained. Its capsule was from 0.5 to 1 cm. thick and appeared to be composed of white fibrous tissue clearly demarcated from the surrounding, compressed hepatic substance. There were 2000 cc. of ascitic fluid. Chronic and healed ulcers of the ascending colon also were seen. Evidence of pylephlebitis was not found.

Microscopically, the capsule of the abscess consisted of old, fibrous connective tissue, which in its outer part contained bile ducts and the vascular structures of the liver, and sometimes atrophic clusters of hepatic cells. As the cavity of the abscess was approached the connective tissue appeared younger, until fibroblasts and endothelial sprouts of blood capillaries composed the microscopic fields. In this younger connective tissue there was dense leukocytic infiltration; predominating types were lymphocytes, large mononuclear leukocytes and plasma cells. A layer of fibrin surrounded the abscess cavity in which fibroblasts were developing. In this zone Gram-positive micrococci in short chains were seen. In the exudate

itself considerable necrosis was apparent, but polymorphonuclear leukocytes still persisted.

Gram-Weigert stains of the exudate and of the tissue revealed Gram-positive diplococci, often in short chains.

Comment: The remarkable feature of this hepatic abscess was found in its persistence for so long a time with so little clinical evidence of its presence. Its origin is uncertain. At the onset, abdominal pain, fever, and diarrhea were the only clinical signs, and careful attention then eliminated any specific disease which would account for these manifestations. In its solitary character (Fig. 5) it resembled abscesses of amebic origin, but this could not be proved by examination, either of the abscess or of the intestinal flora. The chronic and healed ulcers of the ascending colon had no specific characteristics by which they could be identified, but the possibility of their being residual from the primary infection had to be considered.

Discussion

From this study it may be concluded that in certain instances, either due to diminished or specific virulence of the microörganisms, or to the specific resistance of the host, pyogenic micrococci may involve the liver in abscess formation which may persist into a chronic granulomatous stage. This characteristic is displayed by these microörganisms in other anatomical situations. There are, for instance, the well known pyogenic granulomas of cutaneous tissues, and the chronic infections of bones in which pyogenic cocci are the causal microörganisms. As far as the liver is concerned, abscesses of long duration, such as those due to ameba, frequently have been emphasized. Attention has been directed previously to the persistence of pyogenic abscesses until they advance into a chronic stage, and also to their insidious progression. That hepatic abscesses, in which the pyogenic cocci are specific etiological agents, induce typical granulomatous changes in the liver such as those which develop in actinomycosis, tuberculosis and blastomycosis, to my knowledge has not been emphasized hitherto. In this series I have reported three cases in which the advance into chronicity was most insidious. These have been of duration, respectively, ten months (Case 6), one year and nine months (Case 7), and two years and nine months (Case 8).

Other cases in which the periods of illness have been shorter have been reviewed in an effort to show the transitional stages between the early and the late cases. These cases present similar characteristics, but are representative of varying degrees of chronicity, and show that the extremely latent stages are but a continuation of the reactions which may exist to some degree in earlier cases.

In only one of my cases was the source of the hepatic lesion without question. In Case 2 there is little doubt that the perforated duodenal ulcer induced the infection from which the hepatic suppuration arose. In three cases, appendicitis was to some extent suggested by the clinical history as having been the starting point for the hepatic abscess. In Case 5 the appendix had been removed five years before onset of the hepatic abscess. In this interval the patient's health was good, and to suppose that a pyogenic focus had persisted for five years, from which the hepatic lesion developed, carries one too far into the speculative field. In Cases 4 and 6 the clinical evidence at first pointed to the appendix, but at autopsy the appendix was found to be but slightly altered. Some evidence existed in both cases of previous disturbance in the appendix, but with healing completed it was impossible to prove beyond question, from pathological studies, that the appendix had been the primary focus of infection. In Cases 5 and 8 there were non-specific ulcerative lesions in the bowel; these could have constituted the focus from which infection of the liver had developed. In Case 6 the question of a primary appendiceal focus with secondary empyema of the right side and extension from that to the liver, appeared to be the clinical course of the illness. It is more reasonable, however, to believe that portal infection was masked by the empyema, and that the empyema was in reality an hepatic complication, by extension of infection through the diaphragm. The evidence of hepatic involvement became apparent as the empyema subsided. The source of the infection in Case 3 presented difficulty in interpretation. There seemed to be a relation between the cervical suppuration and the hepatic abscess, in that one preceded the other. The hepatic lesion, however, had almost unmistakable characteristics of an abscess of portal origin. It is possible and reasonable to assume that secondary foci were established in the lungs at the onset of the final severe illness, when cough was the principal complaint. Secondary distribution of infection could have occurred within the field of portal drainage and a third

focus could have been established in the liver by way of the portal vein. This circuitous route seems necessary to explain all factors, if the cervical infection is to be considered as the source of the hepatic infection. A retrograde route, from the right auricle to the inferior vena cava and hepatic vein, seems untenable.

The hepatic pyogenic granulomas partake of some of the general characteristics which other abscesses of portal embolic origin possess. Karsner,[11] Kaufmann,[2] Rössle,[3] Schwartz,[12] and others have described the abscesses of portal embolic origin as being multilocular in their formative period. The multilocular construction appears to be due to a shower of infected emboli being transported to the liver and localizing in some of the intrahepatic branches of the portal vein. The size of the emboli determines the point of hepatic lodgment and the number of them apparently determines the extent to which the multiple abscesses will form. In cases unassociated with thrombosis of the main or large branches of the portal vein, the actual emboli may not be found even in microscopic preparations, because the small emboli form the centers about which the abscesses develop, and the emboli lose their identity in the field of suppuration very early. This multilocular characteristic is never found in abscesses in which the method of transportation of bacteria is other than through the portal vein. It is always, however, the outstanding characteristic of the hepatic abscess that is known to be disseminated by emboli that pass through the portal circulation. Examination of the abscesses shortly after their formation will show that the limiting encapsulating membrane of each unit of the multilocular abscess is composed only of hepatic tissue. Ordinarily progressive suppuration should dissolve these partitions, and a single cavity results. The partitions in the granulomatous abscesses, however, usually persist to a greater or less degree, and on them the fibroblastic proliferation and other productive reactions ensue (Figs. 6 and 7). The rapidity with which this organizational change in the capsule progresses, apparently reinforcing the original barrier of hepatic tissue, determines whether the suppuration and destruction of tissue will continue to the formation of large multilocular cavities (Fig. 2), or of a single cavity (Fig. 5), or whether through excessive productive tissue reactions the original appearance of multilocularity will be preserved (Fig. 4). In the later stages the trabecular strands which form the capsules for the multilocular units may be identified as

having their formation on the earlier, purely hepatic basis by the recognition of biliary duct structures which persist in them.

I have seen and described two types of pyogenic abscess which may persist into the extremely chronic stages; the one is a solitary cavity (Case 8, Fig. 5) resembling the solitary amebic abscess, and the other the multilocular or honeycomb abscess resembling the lesion of actinomycosis (Cases 6 and 7, Fig. 4). The granulomatous characteristics of each type are similarly manifested in studies on their capsule, but the reaction to formation of solid granulomatous portions, replacing smaller multilocular abscess cavities, was shown only by the latter type. The microscopic characteristics of the pyogenic granuloma in general reveal those features which are grossly evident. There is a fibrous encapsulation which, according to duration, exhibits more old or more young connective tissue. The connective tissue reaction, however, appears to be slowly progressive toward resolution of the abscess. Thus fibroblasts, endothelioid cells, large mononuclear leukocytes, lymphocytes and plasma cells permeate the regions of productive reaction, with giant cells even constituting a part of the picture (Fig. 8). The exudate itself, at first predominatingly of polymorphonuclear neutrophilic leukocytes, becomes gradually transformed into partially necrotic detritus in which many mononuclear types of leukocytes appear. Colonies of micrococci appear abundantly in the earlier cases, but later they are identified only with difficulty. When abundant, either the staphylococci or the streptococci may assume in their colonization features like the actinomyces (Fig. 9); they are easily distinguished, however, by higher magnifications and bacterial stains. That these abscesses represent regressing actinomycosis with disappearance of the actinomyces is barely possible, but in my experience with the disease, such an eventuality does not occur when organic actinomycosis once becomes instituted. Yeasts, fungi, *Mycobacterium tuberculosis*, and so forth have been considered, but a causal relationship for these organisms never has been demonstrated. I have been forced to believe that the demonstrable micrococci are the etiological factors, in spite of the seeming improbability that the pyogenic micrococci could endure in the liver for a sufficient time to produce a specific pyogenic granuloma.

Summary

1. Abscesses of the liver, originating from within the field of drainage of the portal vein, form a significant clinical and pathological group. These usually take origin from primary intestinal foci through the production of local thrombophlebitis. The hepatic suppuration develops from the passage of infected emboli from the primary foci by way of the portal circulation to the liver.

2. The primary thrombophlebitis may induce thrombosis of the portal vein and pylephlebitis, or this feature of the lesion may be absent.

3. As the cases emphasize, the primary focus may be cryptogenic. From the appearance of the abscess, however, the source may be suspected. A characteristic distribution and type of abscess is produced by each method of hepatic dissemination.

4. The abscesses of portal origin are at first multilocular, due to multiple foci in emboli. Each multilocular abscess usually remains discrete, although they may be multiple. Involvement of the right lobe alone is most common. General hepatic dissemination, in this type, is unusual.

5. The significance of the pyogenic cocci as etiological agents has been emphasized. The illness associated with abscess of the liver may be extremely insidious, and as the primary focus may be cryptogenic, so also the hepatic lesion itself may exhibit this same characteristic.

6. Progression into extreme chronicity may occur, with preservation of the original multilocular arrangement, or a solitary, adequately encapsulated abscess may result.

7. In the cases of extreme chronicity a granulomatous reaction has been found, with the pyogenic cocci demonstrable as the etiological agents. Such cases resemble the granulomas of actinomycosis in their chronicity and in their granulomatous characteristics.

8. Eight cases representative of pyogenic abscesses, possessing granulomatous changes in various stages of their evolution, have been presented.

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DESCRIPTION OF PLATES

PLATE 48

FIG. 1. Case 1. Subacute, multilocular, pyogenic abscesses involving the right lobe of the liver, with suppuration progressing locally to actual cavitation. The primary hepatic focus is central. Peripheral dissemination is secondary. Associated thrombopylephlebitis. Difficulty in draining such an abscess is apparent.

FIG. 2. Case 2. Chronic, multilocular, pyogenic abscess of the right lobe of the liver. Large cavities formed by progressive suppuration. Trabecular, fibrotic strands persisting.

FIG. 3. Case 3. Chronic, leaf-shaped, multilocular, pyogenic abscesses of the right lobe of the liver.

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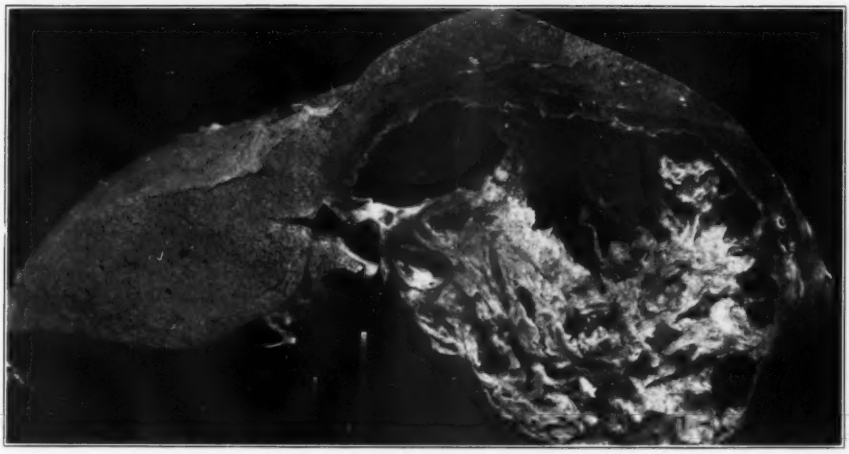


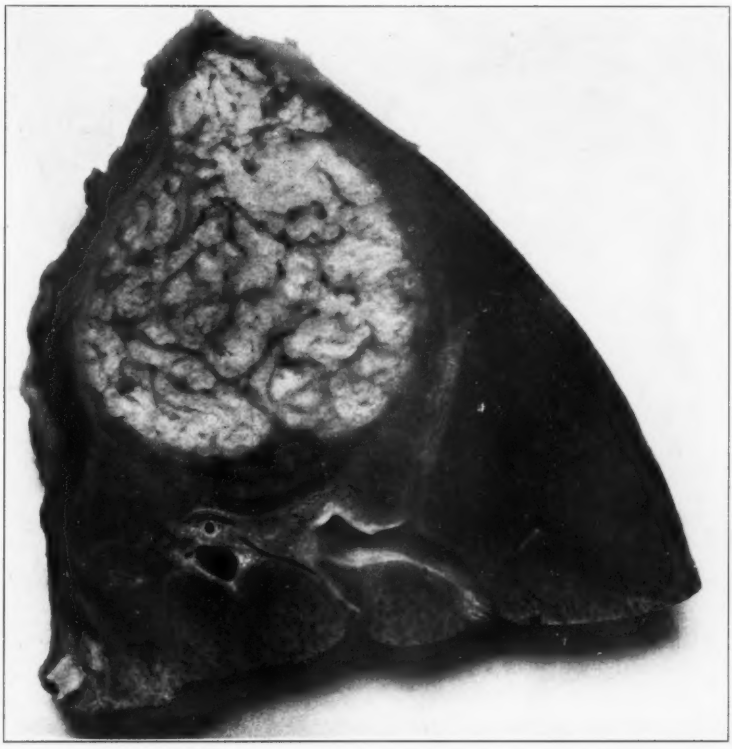
3

Beaver Granulomatous Abscess of Liver of Pyogenic Origin

PLATE 49

FIG. 4. Case 7. Chronic, multilocular, pyogenic abscess of the right lobe of the liver. Scanty suppuration, granulomatous features predominate.

FIG. 5. Case 8. Large chronic, solitary, pyogenic abscess of the right lobe. Dense granulomatous encapsulation.



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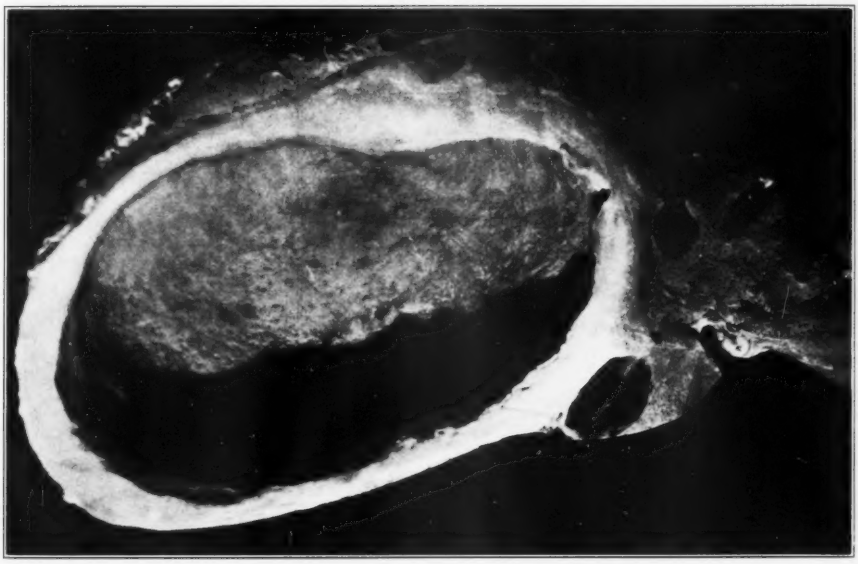

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Beaver Granulomatous Abscess of Liver of Pyogenic Origin

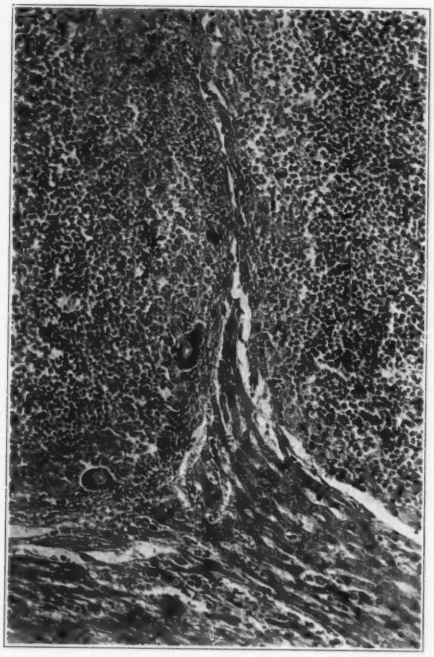
PLATE 50

FIG. 6. Case 2. Two units of a multilocular abscess with persisting partition of hepatic derivation, supplemented by early granulomatous reaction in which giant cells are formed (from small secondary foci about large primary abscess). × 140.

FIG. 7. Case 6. Granulation tissue with fibroblasts, vascular sprouts, lymphocytes and mononuclear leukocytes forming the wall of a multilocular abscess unit. × 165.

FIG. 8. Case 7. Late granulomatous reaction with extensive proliferation of fibroblasts, endothelioid cells, giant cells and lymphocytic collections, replacing the detritus of polymorphonuclear neutrophilic leukocytes. × 225.

FIG. 9. Case 2. Colony of staphylococci in center of small abscess assuming morphological resemblance to *Actinomyces hominis*. × 350.



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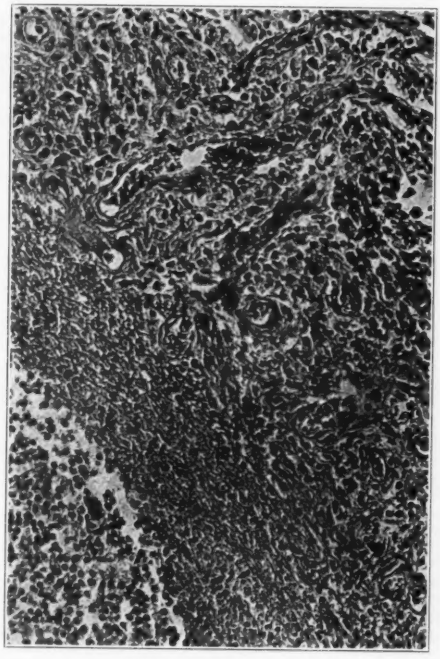

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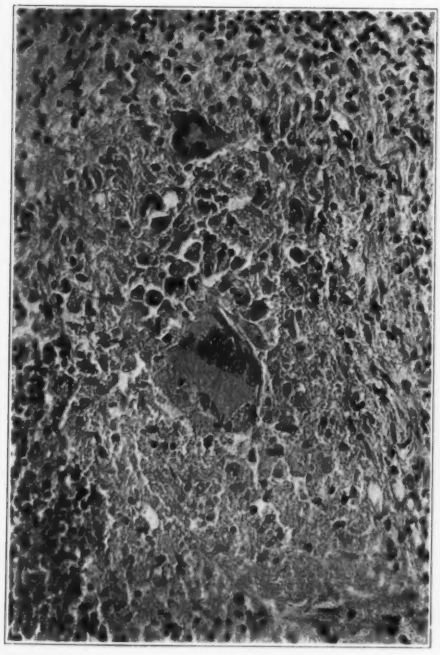

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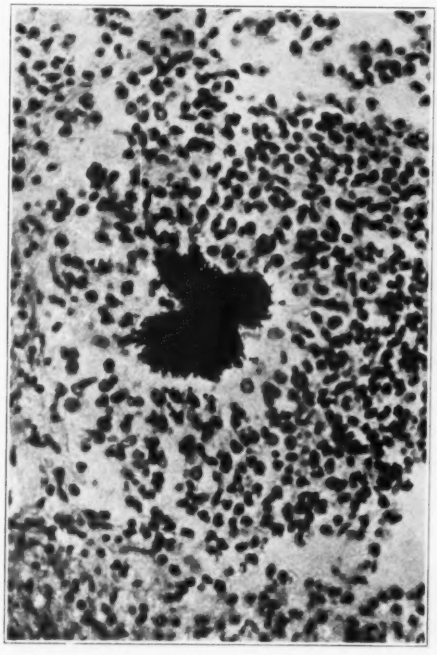
Beaver



9

Granulomatous Abscess of Liver of Pyogenic Origin

ERYTHROBLASTOSIS WITH JAUNDICE AND EDEMA IN THE NEWLY BORN *

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The object of this report is to place on record a histopathological study of six cases of erythroblastosis in which the etiology was obscure and the pathological findings difficult to interpret in the light of present knowledge.

CASE I. ERYTHROBLASTOSIS WITH JAUNDICE

Clinical Note: Male infant born at 2 P.M. Nov. 3, 1930, after a normal labor of ten hours' duration. Baby breathed and cried well, took warm water well, but showed a moderate degree of jaundice. On the second day he began to vomit yellowish brown fluid. There was no cyanosis and no convulsions. On the third day he vomited yellowish fluid, and later bright red blood. The urine was blood-stained. Marked dyspnea was present beginning on the second day. Death occurred sixty-two hours after birth. Mother and father living and well. This was the fourth child. Three siblings living and well. There was no history of tuberculosis, cancer or lues.

Postmortem Examination: White male infant 49 cm. in length. Development and nutrition both good. No edema. The skin showed moderate generalized icterus. A little frothy, serous, slightly bloody fluid flowed from the nostrils when pressure was applied to the chest. The sclerae were markedly jaundiced. Pupils regular, round and equal, 3 mm. in diameter. Small excoriations in both inguinal regions, more marked on the left. Subcutaneous fat moderate in amount and icteric. Musculature well developed. All the organs had a moderate icteric tinge. Liver extended 6.5 cm. below the xyphoid. Spleen extended 4 cm. below the costal margin. The dome of the diaphragm came to the level of the fourth rib on the left and the third intercostal space on the right.

Pleural Cavity: Negative.

Mediastinum: Contained a thymus weighing 8 gm.

Pericardial Cavity: Contained a few centimeters of slightly icteric fluid in which a few flakes of a material resembling fibrin were floating. A smear of this was found to be negative. Surfaces smooth, glistening and free from hemorrhage.

Heart: Weighed 26 gm., (normal weight 17 gm.). The valve measurements were as follows: tricuspid valve 3.8 cm., pulmonary valve 2.2 cm., mitral valve 3 cm., and aortic valve 2.1 cm. The myocardium of the left ventricle measured 0.6 to 0.7 cm., and the right measured 0.3 cm. On the posterior surface of the heart were a few scattered petechial hemorrhages, none exceeding 2 mm. in diameter. The myocardium was reddish brown in color. Foramen ovale and

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ductus arteriosus both patent, the former measuring 5 mm. and the latter 3 mm. in diameter. Interventricular septum intact. Valves and endocardium negative.

Lungs: Right lung weighed 46 gm. and was moderately well expanded. The left weighed 38 gm. and was well expanded. Pleural surfaces of both lungs smooth and glistening, but showed scattered petechial hemorrhages measuring up to 2 mm. in diameter. Scattered throughout both lungs, particularly in the dependent portions of both lower lobes, were frequent dark brown hemorrhagic areas which measured up to 2 cm. in diameter. Crepitation reduced in these areas. Slight emphysema noted in the non-dependent portions. A large amount of frothy, serous yellow fluid could be expressed from all portions of the cut surface by pressure. Bronchial mucosa slightly congested.

Spleen: Weighed 48 gm., (normal weight 8 gm.). Grayish purple in color and speckled with diffuse gray areas. External surface showed much slight puckering but no inflammatory exudate. Thin sections cut easily and held their shape well. Cut surface a rich reddish brown in color and firm. Malpighian corpuscles could be distinguished but were not enlarged.

Pancreas: Negative.

Gastro-Intestinal Tract: Mucosa of the stomach moderately congested. Small and large intestines contained a very small amount of meconium.

Liver: Weighed 190 gm., (normal weight 78 gm.). Capsule smooth, glistening and not thickened. Liver dark uniform purplish brown in color. Consistence appeared to be normal. No evidence of fatty infiltration or biliary stasis.

Gall-Bladder: Negative.

Adrenals: Together weighed 10 gm. Negative.

Kidneys: The right kidney weighed 19 gm. and the left 19 gm., (normal weight of right kidney 13 gm., left 14 gm.). Cortex measured 2 mm. in thickness. Negative except for fetal lobulations and reddish brown uric acid deposits in medulla.

Bladder: Showed several small submucous hemorrhages measuring up to 0.5 mm. in diameter.

Genitalia: Normal in size and development for this age period. Both testicles descended.

Aorta: Elastic, and the whole intimal surface markedly icteric.

Organs of the Neck: Trachea, thyroid, submaxillary glands and a small portion of jaw removed. These structures were negative.

Bone Marrow: Sections were taken from the ribs and vertebrae. Marrow reddish brown in color, indicating active hematopoiesis. Costochondral junction slightly irregular in outline, but sharp and well defined.

Spinal Cord: Sectioned transversely at intervals of 1 to 2 cm. Negative throughout.

Brain: Weighed 368 gm., (normal weight 335 gm.). Diffuse icteric tinge and a few petechial hemorrhages into the fossa interpeduncularis. Anterior fontanelle measured 3 by 6 cm. in diameter. No posterior fontanelle seen. Meninges negative. Arachnoid fluid present in normal amount and clear. There was no pressure cone. Brain uniformly firm after fixation in formalin. Coronal sections were made at intervals of 1 to 2 cm. The substance of the brain, particularly near the base and near the ventricles, showed moderate jaundice.

Bacteriology: Pneumococcus recovered from the peritoneal cavity.

Microscopic Examination

Heart: Essentially negative.

Lung: Showed many small hemorrhages, chiefly intra-alveolar. A few of the extravasated red blood cells were nucleated. A few alveoli contained polymorphonuclear leucocytes and macrophages. Others showed bits of vernix and a few cornified epithelial cells. The interlobular connective tissue septa were edematous and infiltrated by a few macrophages. There was moderate postmortem desquamation of bronchial epithelium. Many bronchial lumina contained red blood cells.

Spleen: Moderate congestion was present and there was marked hematopoiesis in both the erythroblastic and myelocytic series, with the former predominating. A moderate number of pigment-laden macrophages were observed. There was no hemorrhage, necrosis or increase in connective tissue and no acute inflammatory cell infiltration. Follicles were not hyperplastic. The section stained by Levaditi's method showed no spirochetes.

Pancreas: Pancreatic interstitial connective tissue was slightly but definitely increased and somewhat edematous. It showed very slight hematopoiesis.

Gastro-Intestinal Tract: Negative.

Liver: The outstanding feature was marked embryonic hematopoiesis in which both myelocytes and normoblasts were represented, with the latter greatly predominating. The liver cells were well preserved, but showed a number of small fatty vacuoles. The bile capillaries were not dilated and the bile ducts were well preserved. No spirochetes were found.

Adrenals: Numerous foci of hematopoiesis were seen in various parts of the sections.

Kidney: In the medulla of both kidneys next to the pelvis were several small to moderate sized discrete and confluent abscesses with necrosis. Hemorrhages into the abscess had also taken place. Moderate generalized congestion was present, particularly in the medulla, and the vessels contained many nucleated red blood cells and frequent myelocytes. A few tubules contained uric acid crystals. The glomeruli were normally formed.

Thymus: Showed moderate hematopoiesis in the edematous interlobular stroma, and slight hematopoiesis in the thymic parenchyma.

There were numerous Hassall's corpuscles, some of which were unusually large.

Thyroid: Only occasional follicles showed intact epithelial cells and the presence of a small amount of colloid. The majority of the acini were devoid of colloid.

Bone Marrow: Active hematopoiesis was indicated by the presence of frequent myelocytes, erythroblasts, normoblasts and megakaryocytes. The line of provisional ossification was sharp and well defined and many of the bone trabeculae near it were incompletely ossified. There was slight irregularity of the columns of cartilage cells next to the line of provisional ossification.

Brain: Negative.

Cord: A few widely scattered macrophages were found in the meninges.

SUMMARY: This was an infant who died at the age of 62 hours, with the clinical diagnosis of hemorrhagic disease of the newly born. The main signs had been bleeding from the mouth and nose, and blood-stained urine. Icterus was present. The main postmortem findings can be divided into two groups. There was some evidence of a pneumococcemia as shown by recovery of pneumococcus from the peritoneum, slight bronchopneumonia and multiple abscesses in the kidneys, and in addition there was aspiration of amniotic contents indicative of a certain degree of intra-uterine asphyxia. The second group of findings included icterus, an enlarged spleen and liver, and foci of hematopoiesis in various organs of the body.

CASE II. ERYTHROBLASTOSIS WITH JAUNDICE

Clinical Note: A male child, sixteen hours after a normal birth at full term, developed difficulty in respiration and died suddenly. The total duration of labor was six hours and nothing untoward was noticed at any time. The placenta appeared normal. There were two other children alive and well. The mother's history was entirely negative.

Postmortem Examination: Body was that of a well developed, decidedly icteric male infant, weighing 7½ pounds. Slight edema of the scrotum. Finger nails bluish in color. Umbilical cord showed no evidence of hemorrhage or infection. Fontanelles normal. A slight, reddish, frothy discharge was present around the nose. Subcutaneous tissues moist. The fatty layer measured 0.5 cm. in thickness and was markedly icteric.

Peritoneal Cavity: Negative.

Pleural Cavities: Negative.

Heart: Weighed 35 gm. Foramen ovale patent and measured 1.2 cm. in diameter. Heart muscle dark reddish in color and fairly firm. Valves and endocardium negative.

Lungs: Left weighed 48 gm. and was collapsed. Cut surface showed a patchy congestion in both upper and lower lobes. The bronchi contained a slight amount of reddish frothy material. Right lung weighed 46 gm. and was similar to left.

Spleen: Weighed 47 gm. Capsule smooth and on section cut surface dark red in color and firm in consistence. Malpighian corpuscles not evident.

Pancreas: Weighed 7.5 gm. Slightly reddish in color and fairly firm.

Gastro-Intestinal Tract: The large intestine contained meconium.

Liver: Weighed 208 gm. Right border extended to the true pelvis. Uncut surface as well as cut surface dark red in color and very firm. Gall-bladder was negative.

Adrenals: Combined weight of adrenals 6.5 gm. No evidence of hemorrhage.

Kidneys: Capsule thin. Surface of kidneys red and smooth on section and structure stood out clearly. Right kidney weighed 15 gm. and left 17 gm.

Bladder: Negative.

Organs of the Neck: The thymus weighed 4 gm., reddish gray in color and firm. Thyroid grayish red in color.

Bone Marrow: Red and soft. Femur, vertebra and ribs examined. Epiphyseal line at the upper end of femur well defined.

Spinal Cord: Negative.

Brain: Weighed 275 gm. Negative.

Microscopic Examination

Heart: Negative.

Lung: The alveoli were filled with red blood cells and serum precipitate in many places. Many of the red blood cells were nucleated. A few areas showed a slight emphysema. There was a slight exudate in the bronchi in places, which appeared like a colloid material. The lymph nodes at the hilum showed hematopoiesis.

Spleen: The malpighian bodies were small. The sinusoids and the pulp were congested with red blood cells. Many areas of hematopoiesis were observed, also an occasional mononuclear cell containing hemosiderin.

Pancreas: A few erythroblasts were found in the interlobular septa.

Gastro-Intestinal Tract: Section showed a few small foci of hematopoiesis in the submucosa.

Liver: Showed a great many foci of active hematopoiesis with embryonic blood-forming cells. The nuclei of these cells stained a light blue with eosin-methylene blue. They measured about five microns in diameter and contained two to three chromatin masses

measuring about one micron or less. In addition there were numerous smaller granules which were stained dark blue. The cytoplasm of the cells was stained a very light blue and contained no granules. Surrounding these nodules were many cells which appeared to be erythroblasts, and around the periphery were a few erythrocytes. Myelocytes and occasional myeloblasts were observed between the liver cords which in many places seemed to be compressed. The liver cells and bile capillaries contained considerable masses of yellowish bile pigment.

Adrenals: Showed nodules of hematopoietic tissue.

Kidneys: The cortex and medulla contained an occasional focus of blood-forming cells.

Thyroid: Foci of erythroblastic tissue were found in the thyroid. The follicles for the most part were not fully developed. A very slight amount of colloid was present.

Bone Marrow: Hyperplastic. Primitive blood-forming cells, erythroblasts and myeloblasts predominated. Numerous megakaryocytes were observed also. Very few erythrocytes were found. The stroma of the marrow was very delicate.

Central Nervous System: Sections through meninges and choroid plexus showed small foci of hematopoiesis.

Special Stains: Several sections from heart muscle and liver were made and stained by Levaditi's method with negative results.

Bacteriology: Smears stained by the Gram-Weigert method, and cultures from the lungs, spleen, heart's blood and peritoneal cavity were negative.

SUMMARY: In this case there was marked jaundice with bile stasis in the liver, enlargement of the liver and spleen, slight bleeding into the pulmonary alveoli, and abnormal hematopoiesis in the liver and other organs. There was no abnormality of the biliary tree.

CASE III. ERYTHROBLASTOSIS WITH JAUNDICE

Clinical Note: A well developed female child, after a normal delivery at full term, developed difficulty in respiration and died twenty-four hours later. In view of a slight bloody discharge from the mouth and rectum before death, transfusions were attempted. The mother's history was entirely negative.

Postmortem Examination: Body markedly jaundiced. No gross anatomical malformations observed. Abdomen markedly enlarged. Subcutaneous fat thin, measuring about 2 mm., and decidedly icteric. No excess fluid or blood found in the peritoneal, pericardial or pleural cavities.

Heart: Negative.

Lungs: Lungs appeared normal on surface. On section small foci were observed which suggested atelectasis, and some areas were slightly hemorrhagic.

Spleen: Just visible beneath left lobe of liver and weighed 55 gm. Capsule smooth, and on section cut surface firm and uniformly reddish brown in color.

Gastro-Intestinal Tract: Lower portion of colon contained meconium.

Liver: Weighed 300 gm. and extended 7 cm. below costal margin on the right side in mid-axillary line. Surface firm and dark red in color. Cut surface very firm and dark red in color.

Gall-Bladder: Negative.

Adrenals: Appeared normal in size.

Kidneys: Negative.

Thymus: Appeared slightly enlarged and was covered with a blood clot due to the injection of blood.

Microscopic Examination

Lung: Showed considerable atelectasis. The bronchi in places contained a hyaline-like material which enclosed cornified cells.

Spleen: The spleen showed many dilated capillary spaces which contained numerous blood cells, many of which were hemolyzed. The pulp contained many nucleated red blood cells. In many areas there was considerable hemosiderin, partially free in the pulp and partly in mononuclear cells. The follicles were small but apparently normal in number.

Liver: Showed a marked hematopoiesis. The foci, which were numerous, appeared to be producing various types of red blood cells (erythroblasts and normoblasts). The periportal connective tissue showed hematopoietic activity and numerous myelocytes and myeloblasts were observed. The cytoplasm of the liver cells was very faintly staining and in places in the liver cords and even in the liver cells needle-like brownish masses of bile pigment were observed. The sinusoids were dilated at the expense of the liver cords. A large number of hematopoietic foci were located in the liver cords. Mitotic figures were observed in the erythroblasts. In many places the liver cells appeared to be loaded with fat.

Adrenals: A few foci of hematopoiesis were observed in the cortex.

Kidney: In some areas the cells of the proximal convoluted tubules showed a fine granulation with small vacuoles in the cytoplasm. Foci of hematopoiesis were observed in the kidney and in the wall of the pelvis.

Thymus: Showed active hematopoiesis.

Special Stains: Seven Levaditi preparations from the liver were negative for spirochetes.

SUMMARY: The findings in this case were abnormal hematopoiesis, icterus, partial atelectasis with slight aspiration of vernix and slight bleeding from mouth and rectum.

CASE IV. ERYTHROBLASTOSIS WITH NEITHER JAUNDICE NOR EDEMA

Clinical Note: An infant twelve hours after normal birth at a time estimated to be in the latter part of the ninth month, developed difficulty in respiration and died. The infant was reported to be passing bloody urine prior to death. The mother's history was negative. There was one other child, 2 years old, alive and well.

Postmortem Examination: Body showed no gross anatomical lesion of any nature except an enlarged abdomen. The layer of subcutaneous fat was practically absent.

Heart: Muscle firm and reddish brown in color.

Lungs: Atelectasis observed toward the base. Small portion sank in water.

Spleen: Weighed 90 gm. Capsule smooth and reddish brown in color. On section cut surface firm and uniformly dark red in color.

Pancreas: Normal in size and consistence.

Liver: Weighed 280 gm. Left lobe nearly as large as right. Surface smooth. Capsule not thickened and on section cut surface firm and reddish brown in color.

Gall-Bladder: Negative.

Adrenals: Negative.

Kidneys: Negative.

Bladder and Ureter: The bladder was connected to the region of the umbilicus by the urachus. On section about 1 cc. of bloody fluid observed. Ureters appeared normal.

MICROSCOPIC EXAMINATION

Heart: Heart muscle appeared normal.

Lung: Showed atelectasis. In areas where the lung had expanded some of the alveoli were filled with a homogeneous pinkish-staining fluid. The bronchi showed slight desquamation of epithelium.

Spleen: There were numerous nucleated red blood cells, erythroblasts and myeloblasts in the pulp. The splenic lymph nodules did not stand out clearly.

Pancreas: Appeared normal. Foci of hematopoiesis were observed in the connective tissue around the pancreas and in the connective tissue between the lobes.

Liver: The liver cords contained hematopoietic foci and the nuclei of the liver cells were difficult to distinguish from the embryonic hematogenic cells. Here the liver cells were small and compressed, probably due to the space occupied by the hematopoietic foci, and showed slight fatty degeneration. Numerous eosinophilic myelocytes were observed in the periportal connective tissue along with myeloblasts. In certain areas the liver cells contained fine brownish granules, probably bilirubin. There were great numbers of erythroblasts showing mitoses in these sections.

Adrenals: Showed foci of hematopoiesis.

Kidneys: In places the tubules appeared to be plugged with nucleated blood cells. The cells of the proximal convoluted tubules showed a marked pyknosis of the nuclei with a pale staining, swollen cytoplasm. Many areas of hematopoiesis were observed throughout the sections.

Bladder: A few nucleated red blood cells were observed in the submucosa.

Thymus: Showed foci of hematopoiesis.

SUMMARY: The findings in this case were enlargement of the liver and spleen, blood-stained urine, slight degeneration of the cells of the proximal convoluted tubules and abnormal hematopoiesis in the liver, spleen and other organs.

CASE V. ERYTHROBLASTOSIS WITH EDEMA

Clinical Note: Female infant died during birth. The exact time the fetal heart stopped beating was not known. Head impacted and presentation transverse. The mother was a multipara in good health and with a negative history.

Postmortem Examination: A full term, female white infant, weighing 7½ pounds. Marked pitting edema of entire body, most marked in the upper part. Hair on the scalp unusually abundant and dark colored. Subcutaneous tissues over the chest and abdomen 8 to 12 mm. in depth. Their thickness was due largely to edema. Pectoral and abdominal muscles greatly swollen, pale yellowish gray in color.

Peritoneal Cavity: Contained a large amount of clear straw-colored fluid, estimated to be about 500 cc.

Pleural Cavities: Each contained about 150 cc. of clear straw-colored fluid.

Mediastinum: Contained a thymus of average dimensions estimated to weigh about 4 gm.

Pericardial Cavity: Slight increase in fluid, approximately 25 cc.

Heart: In both visceral and parietal layers of pericardium were a few petechial hemorrhages varying from 1 to 1.5 mm. in diameter. Myocardium rather pale but normal in consistence. Endocardium and the heart valves negative.

Lungs: Collapsed, and filled approximately half the chest cavity. Firm and rubbery in consistence, dark reddish purple in color.

Spleen: Weighed 22 gm. Firm in consistence and dark red in color.

Pancreas: Negative.

Gastro-Intestinal Tract: Stomach contained a mucinous material. Lower part of small intestine contained a considerable amount of fluid and greenish black meconium.

Liver: Firm and weighed 150 gm. Cut surface rusty brown and lobules could not be made out.

Gall-Bladder: Negative.

Adrenals: Negative.

Kidneys: Negative.

Bladder: Negative.

Uterus, Tubes and Ovaries: Negative.

Aorta: Negative.

Organs of the Neck: Thyroid very small, each lobe being about 8 mm. in its greatest dimension.

Bone Marrow: Bright red color in ribs and vertebra.

Spinal Cord: Appeared entirely negative in lumbar region.

Brain: Beneath the scalp was a collection of clotted blood and serum about 1 cm. in depth. Sutures almost completely closed. Posterior fontanelle completely closed, while the anterior fontanelle measured 1.5 cm. in its greatest length, and 8 mm. in its greatest diameter. Cerebral venus sinuses distended with clotted blood.

Microscopic Examination

Heart: Negative.

Lung: The lungs were unexpanded.

Spleen: The spleen showed active hematopoiesis. The pulp was congested with cells and contained numerous embryonic cells of the red blood series and numerous normoblasts and erythrocytes. The lymph follicles were small.

Pancreas: Showed foci of hematopoiesis.

Intestine: The duodenum showed numerous small foci of nucleated red blood cells in the submucosa.

Liver: Numerous foci of blood-forming cells were scattered through the liver parenchyma. These foci contained from one to two dozen cells. The nucleus of these cells was slightly larger than an erythrocyte and was composed of a clear staining background in which about a dozen chromatin masses were spread, more particularly around the periphery of the nucleus. The cytoplasm immediately around the nucleus was basophilic in staining reaction and gradually faded in intensity until the border of the cell was indistinct. Mature erythroblasts were present and also numerous normo-

blasts. The erythroblasts showed a slight acidophilic cytoplasm and the nucleus stained a dark blue.

The capillaries were slightly dilated and contained many red blood cells. The liver contained a great amount of bile pigment which was for the most part in the liver cells. The periportal areas showed many eosinophilic myelocytes.

Kidneys: The vessels were congested. Numerous small foci of blood-forming cells were observed in the cortex.

Adrenals: Negative.

Bladder: Negative.

Lymph Nodes: The mesenteric lymph nodes showed active hematopoiesis.

Thymus: Showed marked blood formation.

Thyroid: Showed marked hematopoiesis. The follicles were not well differentiated and contained a slight amount of colloid.

Esophagus: Negative.

Bone Marrow: The spinal column, rib and femur showed active hematopoiesis. Great numbers of erythroblasts and immature red blood cells were observed, also myeloblasts, myelocytes and megakaryocytes. Bone formation appeared normal.

Brain: The vessels of the cortex showed some congestion.

SUMMARY: This is a case in which death occurred at birth. The anatomical findings were a generalized edema, moderate enlargement of the liver and spleen, petechial hemorrhages in the scalp and pericardium, unexpanded lungs and numerous foci of hematopoiesis in the liver and other organs.

CASE VI. ERYTHROBLASTOSIS WITH EDEMA

Clinical Note: A female fetus in the ninth month was delivered dead by Cesarean section. The fetal heart was not heard after birth and the cord was not pulsating. The mother had quite marked hydramnios. Otherwise the history was entirely negative. This was the second confinement; another child, 3 years of age, was alive and well.

Postmortem Examination: Body well developed and weighed 4¾ pounds. Total length 40 cm. The striking feature about the body was the edema which was generalized and very marked. Abdomen distended and flat on percussion. Skin appeared normal. There was a considerable growth of dark coarse hair. Scalp edematous, also eyelids and face. Subcutaneous tissue very edematous and measured 1 to 2 cm. in thickness over sternum.

Peritoneal Cavity: Contained 200 cc. of clear thin fluid.

Pleural Cavities: Each contained about 100 cc. of clear thin fluid.

Pericardial Cavity: Slight increase of clear, light straw-colored fluid, about 20 cc.

Heart: Muscle somewhat soft in consistence, otherwise negative.

Lungs: Collapsed and rubbery. Surface pale reddish brown in color.

Spleen: Weighed 25 gm. Quite firm, and on section pulp appeared slightly grayish red and in places somewhat soft.

Pancreas: Negative.

Gastro-Intestinal Tract: No bleeding into the intestinal tract. Cecum on the left of the midline.

Liver: Weighed 170 gm. and filled practically the whole right half of abdominal cavity. Dark red in color and fairly firm. Gall-bladder appeared normal.

Adrenals: Negative.

Kidneys: Each weighed between 4.5 and 5 gm. Negative.

Bladder: Negative.

Genitalia: Negative.

Aorta: Negative.

Organs of the Neck: Thymus weighed 4 gm. and extended to the lower part of the aortic arch. Thyroid small, reddish in color and on section there was no evidence of colloid.

Bone Marrow: Ribs and femur dark red. Epiphyseal lines regular and clearly defined.

Spinal Cord: Negative in the lumbar region.

Brain: Cortex extremely soft. Fontanelles open, the posterior admitting the tip of the little finger, the anterior admitting the tips of the first two fingers.

Microscopic Examination

Heart: The vessels contained numerous nucleated red blood cells.

Lung: Unexpanded. Occasional nucleated red blood cells were observed in the stroma about the blood vessels and bronchi.

Spleen: The capsule was thin, the trabeculae were quite delicate and did not stand out. The malpighian corpuscles were small and the pulp in general was congested with erythrocytes and hematopoietic foci.

Pancreas: The stroma between the acini was dotted with hematopoietic foci.

Gastro-Intestinal Tract: Occasional groups of nucleated red blood cells were observed in the submucosa.

Liver: The liver cells were well differentiated although the outline was not distinct in most areas. The sinusoids and the blood vessels in the portal areas contained numerous erythrocytes and nucleated red blood cells. Very few polymorphonuclear leucocytes were observed. Innumerable small foci of hematopoietic cells with dark staining nuclei containing a dozen or more large chromatin

masses were observed. The nucleus was on the average slightly smaller than a mature erythrocyte, about 6 microns. The cytoplasm stained blue and the whole cell averaged about twelve microns in diameter. The foci contained from two to a dozen or more of these cells scattered throughout. Erythroblasts were observed at the periphery of the foci. In portal areas, especially where the vessel wall was thinned out, a thin layer of endothelium was all that separated the lumen from foci of the cells already described. The portal areas contained a large number of myelocytes.

Adrenal: Nucleated red blood cells were scattered through the cortex, especially near the surface.

Kidney: The smaller vessels were congested. Nucleated red blood cells were observed, especially in the medullary portion, and also occasional small foci of hematopoiesis.

Bladder: Negative.

Thymus: Showed active hematopoiesis. Many cells of the red blood series were observed. Particularly prominent were the myelocytes. Polymorphonuclear leucocytes and normoblasts were observed in fairly large numbers.

Thyroid: There was no colloid. The acini were not fully developed and the stroma contained hematopoietic foci.

Bone Marrow: Showed active hematopoiesis. There were many erythroblasts, myelocytes and megalokaryocytes.

Brain: The vessels of the choroid plexus were loaded with nucleated red blood cells.

Special Stains: Seven sections of heart and of liver were stained by Levaditi's method with negative results.

SUMMARY: In this case no developmental anomalies were observed. There was no evident relationship between the hydramnios and the edema. The findings were the generalized edema, extramedullary hematopoiesis and degeneration of the tubular epithelium of the kidney.

REVIEW OF CASES

In reviewing the pathological findings of the cases reported here one finds that the abnormal extramedullary hematopoiesis was the outstanding feature. This feature was common to all cases and was most strikingly portrayed in the sections of the liver. In each instance the spleen and liver were enlarged. The bone marrow was

examined in four cases and in each case there was active hematopoiesis. Cases I, II and III showed jaundice which was extreme in Case II. In Cases V and VI there was a generalized edema.

From the table it will be noted that these cases have certain features in common with well known clinical conditions of infancy and early childhood. There was slight bleeding from the mouth and rectum in Case III, and blood-stained urine in Case IV. Cases I and V showed many small petechial hemorrhages. These findings suggest hemorrhagic disease. On the other hand, in hemorrhagic disease the bleeding is frequently massive in amount and the organs appear practically normal, while in the condition described here the liver and spleen were greatly enlarged and the bleeding was very slight. Furthermore two cases showed generalized edema, and three showed jaundice. The histological picture of the liver, spleen and other organs separates beyond reasonable doubt this group of cases from hemorrhagic disease of the newly born.

Normally at birth the liver has completely ceased to function as a hematopoietic organ. In congenital syphilis the liver frequently shows hematopoietic activity at birth. This is usually accompanied by a retardation in differentiation of the organs. It is stated by Bullard [1] that the hematopoietic activity compensates for more or less fibrosis of the bone marrow. In the cases described here the bone marrow showed active hematopoiesis, also the lack of clinical or pathological evidence definitely excludes that disease.

The marked enlargement of the liver and spleen, which in Case IV was over eleven times larger than normal for a newly born infant, and the active hematopoiesis in the bone marrow, liver, spleen and other organs strongly suggest that these cases may be related to the "anemias" of infancy and early childhood. Schridde [2] has pointed out the resemblance in cases of hydrops congenitus with marked extramedullary hematopoietic activity to *anaemia pseudo leukemia infantum*. In Cooley's congenital erythroblastic anemia the main anatomical features are the spleen and bone marrow. Quoting directly from Cooley's description,[3] "The greatly enlarged spleen in which the capsule is often thickened, is usually dark red and is tough and tenacious. Signs of perisplenitis are often seen. The spleen is poor in follicles which have been crowded out by the increase of the pulp in which erythropoietic or myeloid areas may be present. Both liver and spleen show in varying degrees an increase

TABLE I

Summary of Findings in Six Cases of Erythroblastosis

Case	Fetal age	Postnatal age	Important clinical features	Liver		Spleen		Microscopic findings
				Gross appearance	Weight (normal weight 78 gm.)	Gross appearance	Weight (normal weight 8 gm.)	
					gm.		gm.	
I	Full term	62 hours	Jaundice, infection	Enlarged and firm	190	Enlarged and firm	48	Embryonic hematopoiesis in liver, spleen, pancreas, adrenals, thymus and lymph nodes. Active hematopoiesis in bone marrow
II	Full term	16 hours	Intense jaundice	Enlarged and firm	208	Enlarged and firm	47	Marked embryonic hematopoiesis in the liver, spleen, pancreas, kidney, adrenal, thymus, thyroid and lymph nodes. Hyperplasia of bone marrow. Capillary bile stasis
III	Full term	24 hours	Moderate jaundice, slight bloody discharge from mouth and rectum	Enlarged and firm	300	Enlarged and firm	55	Marked embryonic hematopoiesis in the liver, spleen, pancreas, kidney and thymus. No demonstrable bile stasis
IV	Latter part of ninth month	12 hours	No jaundice, no edema, bloody urine	Enlarged and firm	280	Enlarged and firm	90	Marked embryonic hematopoiesis in the liver, spleen, pancreas and kidney
V	Full term	Died during birth	Marked generalized edema	Enlarged and firm	150	Enlarged and firm	22	Embryonic hematopoiesis in the liver, spleen, pancreas, kidney, thymus, thyroid and lymph nodes. Bone marrow showed active hematopoiesis
VI	Ninth month	Delivered dead by Cesarean section	Marked generalized edema	Enlarged and firm	170	Enlarged and firm	25	Marked embryonic hematopoiesis in liver, pancreas, kidney, adrenals, thymus. Active hematopoiesis in bone marrow

in interstitial connective tissue. Some observers have laid weight on the presence of nucleated red cells and myelocytes in the liver. The bone marrow is usually hyperplastic and the cortex thin."

This description is quoted at some length because the group of cases described in this report closely resemble the anemia described above in some respects, yet there are important differences between the two conditions. In Cooley's erythroblastic anemia the enlarged spleen and the hyperplastic bone marrow are the main features, while in the cases described here the enlarged liver showing marked embryonic hematopoiesis is an important feature. The spleen is enlarged and shows active hematopoiesis and the capsule is thin and smooth. There is no increase in interstitial connective tissue in the liver or in the spleen. In three of the cases jaundice was present at birth and in two cases there was a generalized edema at birth. The bone marrow in each group of cases showed active hematopoiesis. Cooley's anemia is a disease chiefly of infancy and early childhood, while the infants described in this report died during birth or shortly after, which suggests the possibility that it is a disease condition in which extra-uterine life is impossible.

In order to rule out the possibility of prematurity entering into this condition, nine cases diagnosed prematurity were selected from the autopsy records of the Children's Hospital and the protocols and sections were studied. In three there was no hematopoietic activity in the liver. Six which showed hematopoietic activity in the liver and in the spleen were compared with the cases described in this report. In these six premature infants there were a few foci of hematopoiesis composed of hemoglobin-containing cells which appeared to be normoblasts with an occasional erythroblast. The difference is very striking when one considers that in premature infants which range from the seventh to the ninth month a slight extramedullary hematopoietic activity is found, while in the cases described here, all at or nearly at full term, showed marked extramedullary hematopoiesis with embryonic cells forming the nucleus of the foci.

Discussion

The condition known as hydrops congenitus and characterized by a widespread generalized edema is very rare. It is, however, by no means a new disease, as cases were described in the seventeenth

and eighteenth centuries. Channing [4] in 1842 reported a case of "dropsy of the foetus" with anemia. Ballantyne [5] in the latter part of the nineteenth century collected about sixty cases from the literature. Some suppose that Hippocrates [6] was speaking of congenital edema when he spoke of the birth of a fleshy fetus — *foetus carnosus*. Many cases have been reported since Ballantyne's series. The more recent include those of Lahm,[7] Oberndorfer,[8] Becker,[9] Gierke,[10] Hueper [11] and others. In spite of all this study, the etiology is still unknown. Many theories have been advanced. Koegel [12] thinks some toxin is the cause of the edema and the proliferation of blood-forming tissues, and suggests lues or nephritis in the mother as a probable cause. Becker thinks the edema is a result of a toxemia of pregnancy. A mechanical basis was thought by Virchow [13] and Osler [14] to be the cause of congenital edema. Recently the mechanical explanation has been put forward by Lahm.[15] Congenital edema may be of mechanical origin, but where no anatomical lesions exist to explain the cause of the edema some other explanation must be sought. Oberndorfer pointed out that in mechanically caused edema there are no changes in the blood-forming tissues.

The appearance of the blood-forming tissues in congenital edema is very interesting. Eichelbaum [16] identified the cells forming hematopoietic foci as erythroblasts and applied the term erythroblastosis to cases of congenital edema with foci of the erythroblasts in the liver and various organs. Erythroblastosis may occur without edema. Pinkerton [17] reported erythroblastosis in a boy, 7½ years of age. He applied this term to a case in which the bone marrow was hyperplastic and the liver, spleen, pancreas, lymph nodes and other organs contained enormous numbers of nucleated red blood cells.

Earlier writers (Sänger,[18] and others) described congenital edema with leukemia. Recently Perez and Jakob [19] reported a case of congenital edema with no anatomical findings which would explain the edema. The blood count was 6,000,000 erythrocytes, 450,000 leucocytes, with numerous eosinophiles, myelocytes and myeloblasts in blood smears. The child lived one-half an hour after birth.

In view of the published data, it appears that the hematopoietic foci may be chiefly erythropoietic and the term "erythroblastosis" applied, or they may be leucopoietic and the term leukemia may be used, or the abnormal hematopoietic picture may occur without the edema.

The bile stasis in the liver cells and bile capillaries in Case I is an unusual finding. Icterus neonatorum is generally thought to be due to an excessive hemolysis of red blood cells following birth. It is thought by Goldbloom and Gottlieb [20] that "icterus neonatorum is a hemolytic icterus which is the result of post natal readjustment from a condition of oxygen unsaturation to a normal saturation." Smith [21] states that icterus neonatorum appears more often when the blood group of the mother and of the newborn infant does not match. It is well known that there is a marked decrease in the number of red blood cells from birth to about the tenth day of life. Mitchell [22] has observed that infants with jaundice do not show lower average erythrocyte and hemoglobin values than those without jaundice.

In Case II of this report there is undoubtedly bile stasis in the liver cells and bile capillaries. This observation seems to point to an obstruction, regardless of the fact that the circulatory and biliary systems show no gross anomalies. Goldbloom and Gottlieb [23] speak of a hemohepatogenous type of jaundice in the newborn due to an increased destruction of red blood cells, causing the liver to produce an excessive amount of bile. Also there may be an extrahepatic formation which would add to the intensity of the icterus.[24] In Case II there may have been an excessive production of bile, but it is evident that the bile is dammed up in the liver cells and capillaries. Examination of the reticular network by a modified Bielschowsky stain does not show any abnormality of bile duct system. Due to the hematopoietic foci the reticular system appears in a meshwork, whereas normally the bile capillaries appear to run in radiating lines in the liver cords. The relationship of hematopoiesis to bile stasis is unknown. It is observed, however, that the liver cords in places are crowded by the hematopoietic foci, which may produce sufficient pressure to obstruct the finer capillaries.

The most striking feature of these cases and the one common to all is the hematopoietic activity in the liver and other organs. The cytoplasm in the cells which compose the central part of the foci take a blue stain. Sabin [25] states that in chick embryos an azurophilic cytoplasm predominates when hemoglobin stains first. The cytoplasm of these cells stains an even blue, which probably indicates that they are not hemoglobin-containing and are more embryonic than the erythroblasts which show an acidophilic tint to the

cytoplasm. They correspond to the lymphocytoid wandering cell of Maximow [26] or the primitive mononuclear cell of Pappenheim.[27] No explanation can be given for the early embryonic character of the blood formation. Sure, Kik and Walker [28] have shown that young albino rats develop a marked disturbance in hematopoietic activity when suffering from a deficiency of vitamin B. Normally in the bone marrow, the erythroblasts are the youngest cells found and one megaloblast is sufficient to form a focus of erythroblasts.[29] The finding of widespread extramedullary hematopoietic foci which contain cells more embryonic than the erythroblast must be considered quite abnormal.

The selection of a term descriptive of the hematopoietic picture offered some difficulty. Erythroblastosis was used by Eichelbaum to describe the hematopoietic picture in the liver and other organs in hydrops congenitus. Pinkerton used the term in the connection previously stated. The question arises whether the cells of the hematopoietic foci are not more embryonic than the erythroblast. The hemocytoblast of Ferrata is an undifferentiated cell capable of developing blood cells. The early embryonic cells described in the six cases of this report suggest the hemocytoblast. Warren [30] has used the term hemocytoblastoma to describe a malignant tumor of the kidney pelvis with elements simulating bone marrow, and in many places the central cells of the hematopoietic foci in the cases reported here appear similar to the cells of the tumor he described. However, in these six cases the great number of cells which have differentiated to the point of accurate recognition belong to the erythrocyte series. It appears that the tendency of the cells of the hematopoietic foci in the various organs is essentially erythrogenic.

Summary

1. In the six cases reported, all of which died during birth or shortly after, a detailed description of the pathological findings has been given. The outstanding feature was the occurrence of abnormal extramedullary hematopoietic activity in full term non-syphilitic infants. In each instance there was a persistence of the fetal mode and location of blood-forming activity without a corresponding retardation in general embryological development. Three cases showed marked jaundice at birth. In one of these, bile stasis was

present in the liver. This may have been due to excessive hemolysis of large numbers of imperfectly differentiated erythrocytes loading the liver cells with bile pigment more rapidly than it could be taken care of by the bile-excreting apparatus. One of the three cases showing jaundice was complicated by an infection, but this was not thought to be related to abnormal hematopoietic activity or to the jaundice. Two cases showed marked edema at birth, which corresponded to the condition known as hydrops congenitus. One case showed neither jaundice nor edema. All cases showed a marked enlargement of the spleen and liver.

2. The features which these cases have in common with well known disease conditions of infancy have been discussed. A few factors which are thought to be of etiological significance have been mentioned. However, the cause is still unknown.

3. The cases described in this report, when considered as a group, are probably representative of a definite disease entity of the newly born, and whatever the etiology may be, the underlying cause is undoubtedly the same in each instance, whether or not the individual case is characterized by jaundice or edema, or whether both jaundice and edema are lacking.

4. The term erythroblastosis in the newly born is applied to the pathological syndrome described in the six cases reported here because it best depicts the anatomical findings.

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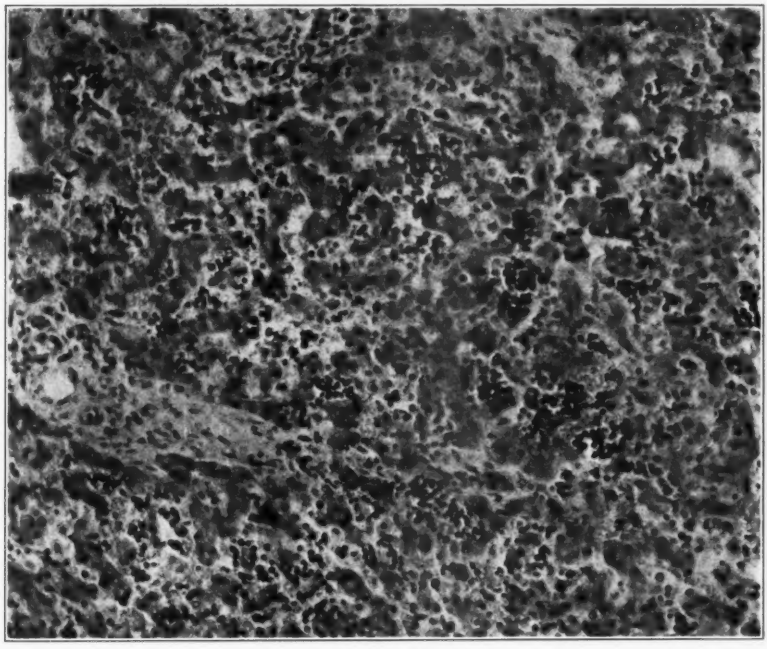
DESCRIPTION OF PLATES

PLATE 51

FIG. 1. Case I. Shows discrete hematopoietic foci and well differentiated liver cells. × 175.

FIG. 2. Case II. Liver. Shows the undifferentiated cells of the hematopoietic foci. The bile stasis in the liver cells is evident. Giemsa stain. × 250.



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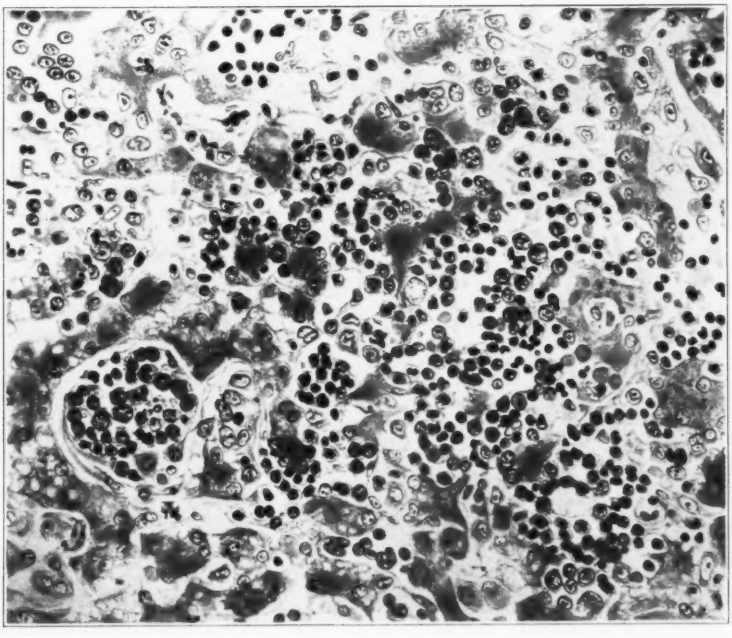

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Ferguson Erythroblastosis in Newly Born

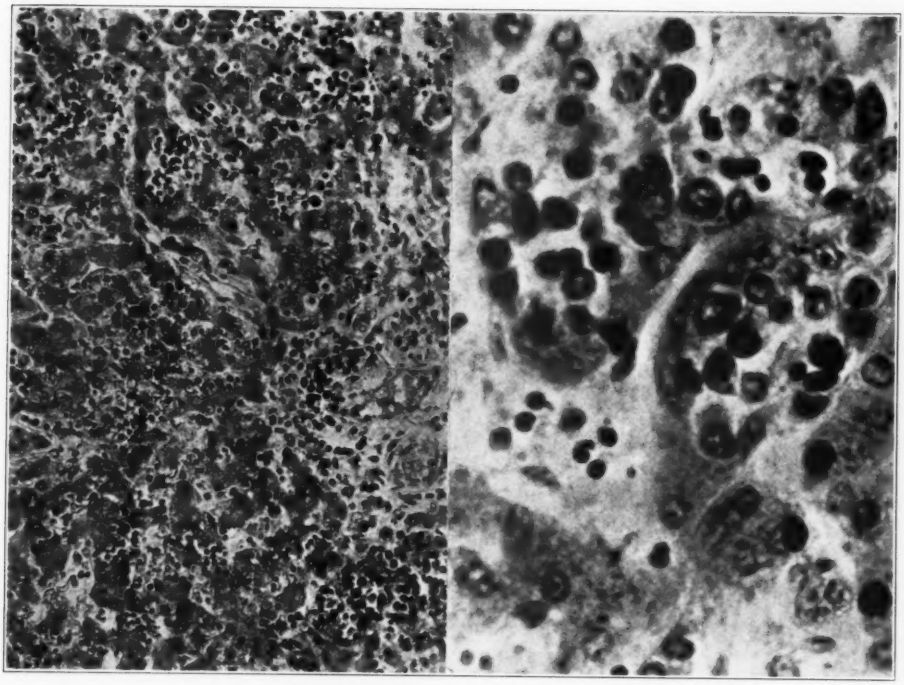
Plate 52

Fig. 3. Case II. Shows active blood formation in the liver. The liver cells are well differentiated. × 150.

Fig. 4. Case II. One small focus of hematopoietic cells. The difference between the mature erythroblast and the more embryonic red blood cells is shown. × 1000.

Fig. 5. Case II. Showing hematopoiesis in the pulp of the spleen and congestion of the sinusoids with nucleated red blood cells. × 750.

Fig. 6. Case II. A hematopoietic focus in the kidney. × 500.



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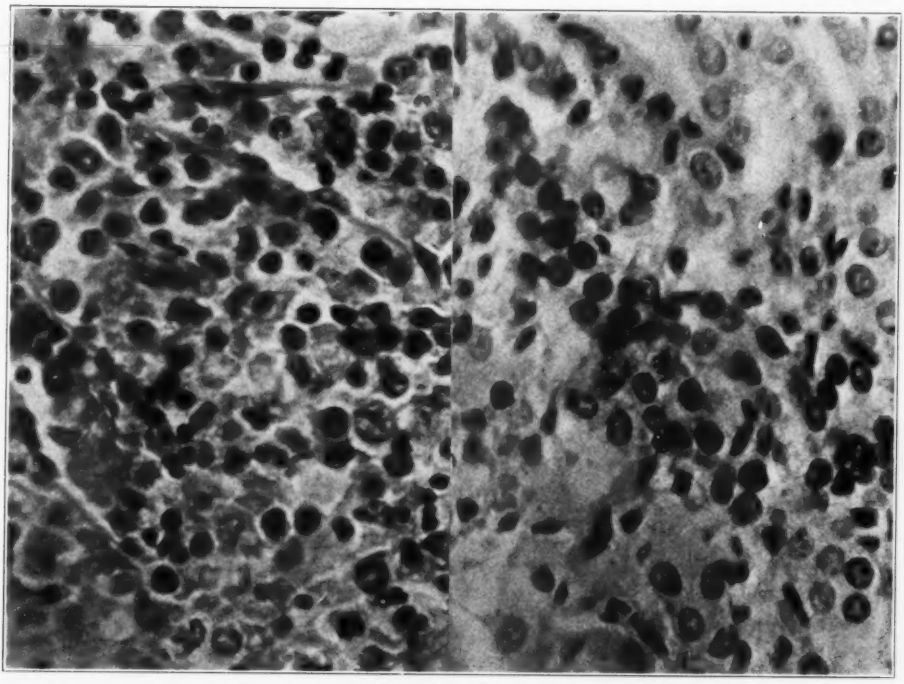


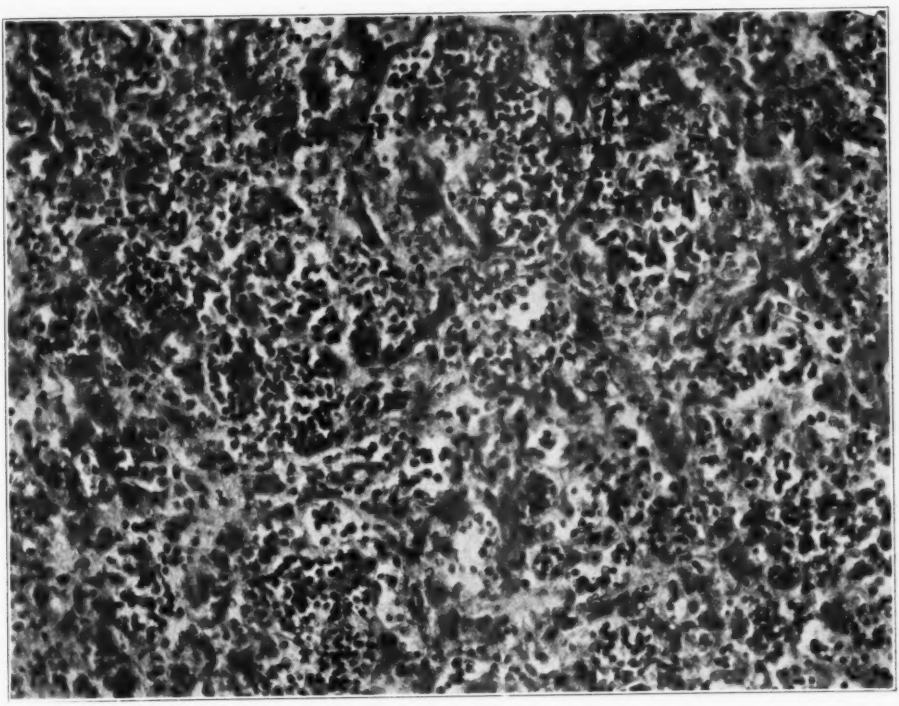
5 6

Ferguson Erythroblastosis in Newly Born

PLATE 53

FIG. 7. Case IV. Shows many hematopoietic foci in the liver. × 175.

FIG. 8. Case IV. Focus of embryonic hematopoietic cells and erythroblasts in the liver cords. × 1000.



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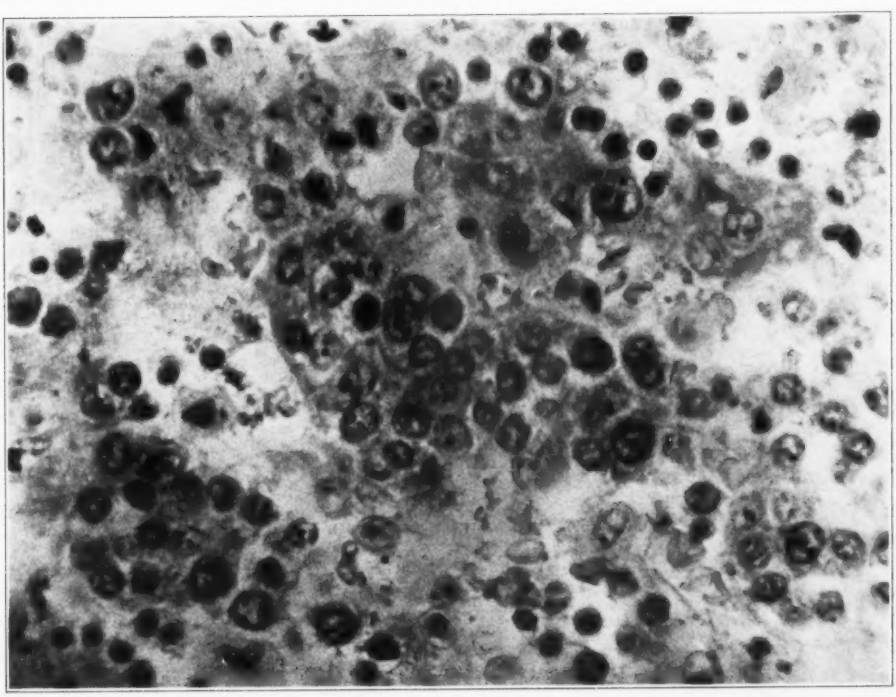

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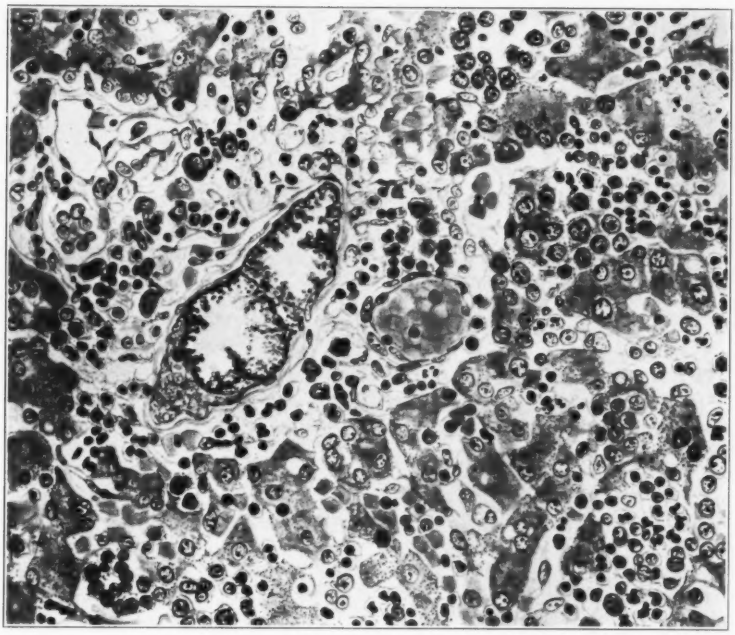
PLATE 54

FIG. 9. Case VI. Liver. The large undifferentiated cells of the hematopoietic foci stand out. The liver cords are well differentiated. The liver cells show fine masses of bile pigment. Eosin-methylene blue stain. × 250.

FIG. 10. Case VI. The photograph was taken after completion of autopsy. The generalized edema is clearly evident.



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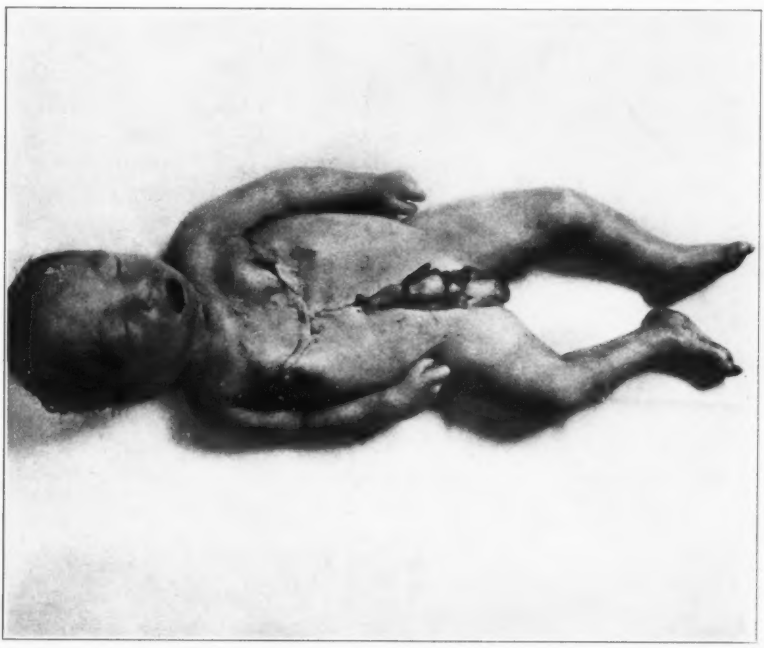

10

Ferguson Erythroblastosis in Newly Born

STREPTOCOCCUS HEPATITIS *

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Infectious lesions of the liver do not play as important a rôle as those of a toxic nature, but they occur in considerable variety, and some of them, syphilis and tuberculosis for instance, are of considerable importance in the pathology of this organ. It is the object of this paper to present several examples of a type of infection of the liver which may not be so infrequent as examination of the literature might lead one to believe. Furthermore, its importance lies in the fact that it may throw light on certain instances of acute yellow atrophy, and on the type of cirrhosis which may follow that lesion if recovery takes place.

The degenerative and inflammatory changes of the liver that may accompany streptococcus infection with and without a septicemia vary considerably and show no one characteristic histological lesion that may be considered as specific for this organism.

Acute Toxic Hepatitis

The more common changes which are found in the liver in cases of streptococcus infection are of a degenerative and inflammatory nature and are usually ascribed to the effect of toxins circulating within the blood stream. These lesions may be distributed diffusely and uniformly throughout the liver, or they may appear quite irregularly. Such lesions as the latter have been described by Helly [1] under the name "septische Leberfleckung." This is characterized grossly by the presence of anemic-like zones throughout the liver. Histologically one sees changes in both the liver cells and endothelial cells. The former are swollen, granular, intensely stained, and frequently distended with fat. The endothelial cells are larger than normal, and show both proliferation and desquamation. The sinusoids contain less blood than the surrounding areas, and the perisinusoidal

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spaces are moderately edematous. A similar histological change may be found throughout the entire liver, and such a picture has been described by Rössle [2] as a "diffuse serous hepatitis."

In instances where the liver has been more severely injured, the liver cells in the central zones of the lobules may show dissociation necrobiosis and necrosis. The last change is not infrequently associated with an extravasation of red blood cells and an infiltration of polymorphonuclear and endothelial leucocytes.

In another group of cases, the changes within the lobule may be negligible, the outstanding lesion being almost entirely confined to the portal areas. Here one finds an acute exudative inflammatory reaction in the portal connective tissue characterized by an infiltration of polymorphonuclear leucocytes, strands of fibrin, edema and swelling of the collagen fibrils. The liver cells bordering this area may show early degenerative changes.

Occasionally one finds an almost pure lymphocytic infiltration of the portal area, a picture first described by Friedreich and von Gaffky,[3] and later spoken of by Virchow [4] as "Lymphome." Rössle regards this lesion as an inflammatory hyperplasia, in the sense of an increased resorptive activity against toxins passing from the damaged lobule into the portal areas.

Whereas we have depicted two rather distinct groups of lesions, one occurring within the lobule and the other in the portal area, we do not imply that both may not be found together — on the contrary this is a fairly common finding. However, to repeat what we have already mentioned, none of these lesions is the result of the actual presence of the streptococcus within the liver, but is due to the presence, either directly or indirectly, of a circulating toxin within the blood stream.

Acute Infectious Hepatitis

Gastou [5] in 1893, in his description of "foie infecté," was the first to point out that a diffuse, acute inflammation of the portal areas was not uncommonly associated with focal intralobular hepatitis, and in a child diagnosed clinically as having diphtheria, which terminated fatally, he demonstrated in the liver both an infiltration of the portal connective tissue and inflammatory foci (containing cocci in chains) within the lobules.

It is with this latter lesion — a lesion described recently by Landé [6] as an "acute focal necrotizing hepatitis" — that we are principally interested in this report, because we believe that in some instances, but not in all, it is the result of the actual presence of the bacteria within the liver.

In the year following Gastou's report, Babes [7] reported four cases of fulminating streptococcus septicemia showing widespread gross and microscopic degenerative and necrotic changes in the liver. In each case streptococci were obtained from the blood, and in all cases but one these organisms were demonstrable in the liver. The histological lesion which he described in three of the cases resembled acute yellow atrophy in the very early stages, showing in addition the sinusoids distended with mononuclear cells containing streptococci. The lobules were made up of trabeculae of large, swollen, granular, eosin-staining, necrotic liver cells. In the fourth case, a patient who had been jaundiced for some time, the liver grossly resembled a later stage of acute yellow atrophy. It was small, shrivelled, soft and red. Histologically much of the parenchyma had disappeared and bile ducts had begun to proliferate and extend into the lobules. Streptococci were neither demonstrable culturally nor in the fixed preparation, although they were recovered from the heart's blood and from several other organs. Babes made no attempt to explain acute yellow atrophy on an infectious basis, but thought that perhaps occasional cases might be of infectious origin. Furthermore, in explaining the absence of streptococci in the liver in the last case he believed that the organism had produced its destructive lesion, and subsequently disappeared.

Bingel,[8] in reporting the pathological findings within the liver in eight fatal cases of scarlet fever, found in two of them irregularly scattered foci of necrotic liver cells infiltrated with an inflammatory exudate. Bacteria were neither isolated nor were they seen within the lesions.

Baginsky[9] reported an interesting case of interstitial hepatitis with widespread but isolated necrosis and inflammation of the liver parenchyma occurring in a child 10 years of age. Clinically it was a picture of a generalized septicemia of ten days' duration, and streptococci were obtained from both blood culture and liver puncture. Grossly the liver was soft, grayish yellow, cloudy and swollen. Syphilis and tuberculosis, as well as such chemical poisons as alcohol

and phosphorus, were definitely ruled out. Smears made directly from the lesions within the liver at the time of the autopsy revealed streptococci. In view of this finding, even though organisms were not demonstrable within the fixed tissue preparations, the author felt that the lesions were probably infectious in origin.

Landé reported two cases of acute focal necrotizing hepatitis, and in both, the lesions varied in size and appeared as grayish yellow areas against a darker background. Microscopically the lesions varied in size from small foci scattered within lobules to much larger areas involving several lobules. These showed dissociation of both reticulum and liver cells, degeneration and necrosis of the liver cells, together with an infiltration of mononuclear leucocytes. Even in the most extensive areas, the vessels and bile ducts together with the interstitial tissue comprising the portal areas were moderately well preserved. Both cases were considered as infectious; streptococcus hemolyticus was recovered from the blood of one of these, but organisms were not demonstrated within the lesions of either.

Aschoff[10] refers to the lesions already described by Landé, and adds that similar lesions may be found in other infectious diseases as well as in streptococcus infection. Furthermore, he points out that probably many foci, often considered as pure necrosis, may be considered in this class.

Rössle, in his description of focal and acute inflammatory lesions of the liver, states that this group of lesions constitutes a relatively uncommon finding, and in autopsies in which one might anticipate these lesions, such as in cases of septicopyemias, they are usually lacking.

Thomson [11] speaks of a type of infectious jaundice in newborn children caused by the streptococcus being carried to the liver from the umbilicus and giving rise to an acute hepatitis. An interesting point which he brings out, and one which has a bearing on one of our cases, is that the umbilicus, although the primary point of infection, may show no external sign of inflammation.

Rolleston,[12] in discussing the etiology of icterus gravis, includes streptococci among the etiological agents in producing the changes within the liver, but feels that the lesion is the result of a generalized toxemia striking a liver that is already lacking in vitality, rather than the direct result of bacteria being present within the organ. He

states that various organisms have been found within the liver but none so constantly as to justify definite conclusions.

One obtains little aid in the study of these acute, non-suppurative, diffuse and focal forms of hepatitis involving the parenchyma of the liver from textbooks of pathology and medicine. Certainly one gains the impression that if streptococci reach the liver they either produce no demonstrable lesion, or an abscess results. Karsner,[13] however, does devote a paragraph to acute non-suppurative inflammation of the liver, in which he describes two types. In one the liver shows cloudly swelling, and histologically one finds an acute polymorphonuclear leucocytic exudate in the portal areas: in the second type, described as acute interstitial hepatitis in contrast to the first which he calls acute parenchymatous, one finds mononuclear leucocytes and lymphocytes instead of polymorphonuclear leucocytes.

The production of abscesses within the liver by the streptococcus is mentioned in almost all textbooks of pathology, and although not a common finding at autopsy it is one that is generally accepted as being beyond dispute. One finds in the literature isolated reports of abscess formation following streptococcus infection; perhaps among the earliest recorded cases is one by Roger [14] in 1896. The patient, a young woman 30 years of age, complained of severe abdominal pain demanding surgical interference. A large abscess was revealed in the tubo-ovarian region from which streptococci were grown in pure culture. The convalescence was poor and the patient died within a few days. An autopsy revealed abscesses in the liver in addition to the pelvic condition. Cultures taken from both sources demonstrated an organism in pure culture similar to that which was obtained a few days earlier at the operating table.

In the more recent literature mention is made by Thomson [11] of the same conditions occurring in children following infection of the umbilical vein.

Before describing the cases which we have found of this acute focal and diffuse non-suppurative type of hepatitis, we wish to consider an entirely different form of hepatitis that is essentially chronic and progressive.

Chronic Infectious Hepatitis

Suggestions of a chronic progressive inflammatory process in the liver going on to form a true cirrhosis and ascribed to streptococci colon bacilli and other bacteria are not infrequently encountered in

the literature.[15, 16, 17, 18, 19, 20, 21, 22] In fact attempts have been made to show that any and all types of cirrhosis could be explained on an infectious basis. Today, however, such an idea seems absurd. The etiological and morphological classifications of cirrhosis have been more accurately determined, and specific lesions of the liver of a chronic progressive inflammatory nature can usually be grouped among the more common and well recognized types of cirrhosis.

Siredey [23] in 1886 described lesions in the liver both degenerative and inflammatory in nature in cases of diphtheria and scarlet fever, and believed that the inflammatory reaction may become chronic and account for certain instances of sclerosis found in later years. He also remarked that patients with an alcoholic history are predisposed to inflammatory lesions within the liver, stating that the alcohol may lower the vitality of the cells, making them more susceptible to infection.

A year later Mogk [24] reported a case of cirrhosis occurring in a young child who, eight weeks before death, suffered a very severe attack of scarlet fever. The liver at autopsy showed irregular areas of necrosis, an inflammatory exudate and a proliferation of connective tissue. The most interesting finding in this case, however, was that chains of streptococci were demonstrated within the more recent lesions.

At a pathological meeting several years later this case of Mogk's was thoroughly discussed by Schlichthorst [25] who, admitting the probability that the changes in the liver were part of the infectious disease, found it difficult to believe that streptococci could persist in the liver for so many weeks.

Henoch [26] was convinced of the important rôle infectious diseases play in the etiology of cirrhosis of the liver. He observed in the very severe cases of measles and scarlet fever signs and symptoms indicative of pathology within the liver. These lesions, he pointed out, could either completely disappear with full restoration of the liver, or could persist long after the acute infection, as an interstitial hepatitis. Histologically he found in such cases a moderate hepatosis, proliferation of the portal connective tissue and dilatation of the small ducts, and looked upon this form of hepatitis as being quite capable of developing into a true cirrhosis.

Folger [27] reported an unusual case of hypertrophic cirrhosis of the liver in a child who had been jaundiced for weeks. The liver was

definitely cirrhotic, and showed advanced sclerosis and a massive production of small bile ducts. Streptococci were demonstrable in the liver and other organs, but were accepted by Folger with considerable doubt as having any direct bearing on the lesion within the liver.

Bingel [8] firmly believed that certain cases of cirrhosis in children, alcohol and syphilis being excluded, could be directly linked up with changes in the liver which may occur in severe epidemics of scarlet fever. He reported a case in a young child, 9 years of age, who had recently suffered a very severe angina, probably of scarlet fever origin, accompanied by pain in the right upper quadrant. The convalescence was poor and seven months later jaundice appeared, together with gastric distress and fever. A few days later the child died. The liver was uniformly firm, sclerotic and irregularly lobulated. Microscopically it resembled somewhat the alcoholic type of cirrhosis, but in addition the fibrosis extended quite often between groups of liver cells. There was a reconstruction of the liver parenchyma, marked increase in connective tissue and a somewhat irregularly distributed, small, round cell infiltration.

Very recently Moon [28] reported two cases showing a progressive type of cirrhosis which he considered as being infectious in origin. One of these occurred in a patient, aged 12 years, who had been diagnosed clinically as having "Banti's disease." The spleen and liver were of about equal size, each weighing just under 1000 gm. The liver, which was firm and nodular, was diagnosed as atrophic cirrhosis. Histologically a section stained for bacteria showed cocci in pairs throughout this organ. The autopsy unfortunately was done a considerable number of hours postmortem; thereby lessening to some extent the importance attributed to these organisms within the liver. The second case was in a boy 14 years of age. The family history is worthy of note in that several of the children had already died from cirrhosis of the liver. This child's spleen and liver were large, and in addition he showed marked anemia, moderate leucopenia, increasing ascites and shortly before death a slight degree of jaundice. No clinical diagnosis was made. At autopsy the liver was large, firm, and showed a hobnail granular surface. Sections of liver tissue showed cocci in areas of more recent degeneration and necrosis, and in addition a pure culture of streptococcus hemolyticus was obtained from the liver at the time of the autopsy.

An attempt to ascribe certain chronic inflammatory lesions of the liver to streptococci, acting locally, is of course open to criticism even where the organism may be demonstrable within the lesions of the liver, since such a bacteriological finding could occur in a terminal bacteremia. Cases assumed to be the result of streptococcus infection, purely on the basis of a clinical history — such cases in which the organisms are not demonstrable, the supposition being that they have died and disappeared — are subject to even greater criticism and can be accepted only with reserve.

Healed Infectious Hepatitis

The last point which we must now consider is the gross and histological changes which one may find in the healed stages of these acute and chronic inflammatory processes within the liver. Where the acute lesions are small there is evidence to show that there is probably complete structural and functional restoration; yet as Rössle says, "we know too little about the fate of these small areas of necrosis and the associated liver changes that may appear with various infectious diseases." The large areas in which all of the liver cells in one or more lobules have been destroyed probably show incomplete regeneration, and heal by sclerosis. Such healed lesions are characterized by the presence of one or more rather sharply circumscribed and irregularly distributed areas composed of connective tissue, bile ducts and regenerated liver tissue; the latter in some cases is entirely absent. This picture, though usually focal in distribution, resembles very closely the healed stage of true acute yellow atrophy of non-infectious origin.

Apropos of this, is an unusual case of cirrhosis, reported several years ago by Rössle,[29] occurring in an elderly male. The liver was quite normal, except for a single isolated area of sclerosis about the size of the palm of the hand lying on the anterior surface of the right lobe. This was irregular, yellowish brown and extended into the liver several finger breadths. Sections from different parts of the liver were carefully examined histologically and except in the areas of sclerosis showed no noteworthy change. The lesion itself showed definite cirrhosis, with reconstruction of the remaining liver parenchyma, increase in connective tissue and bile ducts and a small round cell infiltration. No visible explanation was found for this rather

rare occurrence and the author suggested that it was probably a type of cirrhosis that could be explained on the basis of an embolic toxic-infectious process.

Material for Study

The material which forms the basis for this work was obtained from several of the larger hospitals of Boston, and the cases which are reported below have been selected from several thousand autopsies. We have included only those cases of streptococcus hepatitis which can best be explained as the result of the actual presence of the organism within the liver, and the five cases selected are fairly representative of the types of pathology one may encounter. We have purposely omitted those showing the more common and well recognized degenerative and inflammatory changes so often seen in instances of generalized toxemia of streptococcus origin.

We have considered the lesions in the liver as occurring in three rather characteristic forms: the acute stage with necrosis of liver cells accompanied by a cellular exudate; a chronic lesion showing degeneration and necrosis on the one hand and active proliferation of liver cells, bile ducts and connective tissue on the other; and lastly the healed stage, from which all signs of an active inflammatory reaction have disappeared. As examples of the acute lesion three cases are fully reported. The remaining two cases represent the chronic and healed lesions. We are quite aware of the criticism that may be directed against these latter cases, and for this reason they are presented not as definitely proved examples of what the streptococcus can do, but only as possibilities that may result when the process becomes chronic, and lastly when it has entirely healed.

Case Reports

Case 1. (C. H. A. 28–30), an apparently healthy, white male infant, aged 8 days, developed an abscess near the right wrist. Two days later this was incised and drained. On the third day after the operation the child suddenly developed difficulty in breathing, cried almost continually, and passed five loose green stools during that night. The following morning he was admitted to the hospital dangerously ill. In addition to the lesion on the wrist, an examination revealed signs of bronchopneumonia, a distended abdomen and a protruding umbilicus covered with a pigmented crust. Death occurred a few hours after admission, and an autopsy was performed one and a half hours postmortem.

The peritoneal cavity contained an excess of amber-colored fluid in which were clumps of thick, white, purulent material. Smears of this revealed chains of

streptococci. The wall of the umbilical vein was thickened and the lumen contained pus.

The liver, weight 179 gm., was enlarged and smooth. The sinus venosus was patent, though the wall was thickened and surrounded by a wide area of necrotic tissue extending from the wall into the liver substance. Smaller areas, yellowish red and varying in size from a pinhead to 1 cm. in diameter, were scattered throughout the liver.

The spleen, weight 38 gm., was large, soft and of the septic type.

No noteworthy lesions were found in the heart, lungs and other viscera. The bacteriological examination from both peritoneal cavity and liver was positive for streptococcus hemolyticus.

Anatomical Diagnoses: Acute infectious hepatitis; acute peritonitis; pyophlebitis of the umbilical vein; cellulitis of the right wrist and omphalitis.

Histological Examination

The umbilical vein shows an inflammatory reaction with a fibrinous thrombus attached to its inner surface, and an infiltration of endothelial leucocytes, lymphocytes and plasma cells in its wall.

Within the liver some of the branches of the portal vein are distended with endothelial leucocytes containing numerous streptococci, together with fibrin, polymorphonuclear leucocytes and free streptococci. Many of the smallest branches of the portal vein contain endothelial leucocytes with many streptococci within them.

The liver lobules show scattered foci of hematopoiesis. The outstanding lesion present consists of necrotic liver cells occurring singly and in small groups. They extend to the portal vessels and to the central veins but are most numerous in the intermediate zones. Some lobules show many more of these lesions than others. The necrotic cells tend to stain deeply with eosin and the nuclei are more or less pyknotic. Others have lost their nuclei and are being surrounded or invaded by endothelial leucocytes. In certain areas which may involve one or more complete lobules, all of the liver cells have disappeared, leaving only the stroma infiltrated with numerous endothelial leucocytes. There is no evidence in any of the lobules of a toxic central necrosis, and no abscesses are present.

The most noticeable feature in the sections stained by the Gram-Weigert method is the presence of large numbers of streptococci, chiefly in the endothelial cells lining the sinusoids, but also to some extent within the vessels. In the areas where all the liver cells have been killed off and have disappeared, the stroma is infiltrated with endothelial leucocytes containing fairly numerous streptococci.

In this case the necrosis of the liver cells and the inflammatory reaction are evidently due to the direct action of the toxin liberated by the organisms present in the lesion. This toxin has destroyed the more highly specialized liver cells, leaving the endothelial cells and fibroblasts relatively uninjured.

If the child had overcome this infection and lived, the streptococci and necrotic liver cells would have been removed and the histological picture would then suggest a rather late stage of acute yellow atrophy. In many places only the stroma and portal vessels would have remained, whereas in areas where liver cells had escaped necrosis, regeneration would have occurred. The end result would have been a cirrhosis corresponding to that so often seen following acute toxic hepatitis.

CASE 2. (U 25–23), a female infant who had suffered a prolonged and difficult delivery and died on the fifth day after birth. A postmortem examination disclosed a hemorrhage into the cerebellar fossa, with extension down the spinal canal and out into the loose tissue of the neck.

The liver, weight 150 gm., was normal in size, shape and consistence and dark reddish brown. On the upper surface of the right lobe were two round areas, one 3 cm. in diameter and the other 2 cm. Both were slightly depressed beneath the normal surface, and yellowish brown.

On section these depressed areas were seen to extend about 1.5 cm. into the liver parenchyma. Their yellowish brown cut surfaces were striated with dark red lines suggesting distended capillaries. In consistence, these areas were distinctly softer than the surrounding tissue.

A culture from the heart's blood yielded streptococcus hemolyticus in pure culture.

Anatomical Diagnoses: Infratentorial hemorrhage into cerebellar fossa. Focal necrosis of liver.

HISTOLOGICAL EXAMINATION

Sections from the greater portion of the liver show a few small foci of hematopoiesis but nothing abnormal beyond the presence of small and medium sized fat droplets in some of the liver cells. There is no toxic central necrosis. The two lesions described in the gross examination show a very different condition. Necrosis of liver cells is extensive and in many of the lobules all of them have been killed. In other lobules they remain around central or portal vessels, or are scattered in small groups within the lobule. Masses of necrotic cells are still present and are slowly being invaded and surrounded by endothelial leucocytes and gradually dissolved. The terminal bile

ducts in the portal systems are prominent, but they have not yet begun to grow toward the centers of the lobules. Around them are a few polymorphonuclear leucocytes, eosinophiles and lymphocytes.

Examination for organisms in the fixed preparations, especially for streptococci, was entirely negative.

The decidedly focal character of the two lesions present in the liver strongly suggests that they are of infectious rather than toxic origin. The lesion is in the reparative stage and the causal agent has been destroyed and removed. There remain two foci showing the early healing stages of acute yellow atrophy. In time these would have terminated in areas of sclerosis.

CASE 3. (B. C. H. 01–46), a white female, aged 20 years, was operated on Feb. 2, 1901 and the left ovary removed. On March 16, about six weeks later, at a second operation the right ovary and tube were excised and a diagnosis of acute purulent salpingitis made. Death occurred a week after this second operation and at the postmortem examination made twelve hours later, acute salpingitis of the left tube, a pelvic abscess, and a localized peritonitis of the pelvis were found.

The liver, weight 2320 gm., was much enlarged, smooth and mottled yellowish brown. On section the middle portions of the lobules were yellow and surrounded by narrow red zones.

Cultures from the heart's blood, spleen, kidneys and liver showed a streptococcus.

Anatomical Diagnoses: Pelvic peritonitis, septicemia.

HISTOLOGICAL EXAMINATION

Many of the liver cells contain small to medium sized fat vacuoles; occasionally single large vacuoles are present. Necrosis of liver cells is extensive and diffuse and involves an irregular zone about each portal area from two to ten cells in width, but as a rule leaves one or two rows of cells adjacent to the portal area comparatively uninjured. Viewed in relation to the central vein of the lobule it could be called a zonal necrosis involving principally the periphery of the lobule. Occasionally the necrosis reaches the portal connective tissue, less often it extends here and there to the central vein. There is no evidence anywhere of a toxic central necrosis, even in its earliest stages. The cytoplasm of the necrotic cells is finely granular and strongly eosinophilic. In an occasional normal liver cell adjoining the necrotic zone a mitotic figure can be found. In one section three were grouped closely together.

The necrotic cells are surrounded and to some extent invaded by polymorphonuclear and endothelial leucocytes. The former often collect in considerable numbers but no abscesses are found. They are present also in the portal connective tissue together with endothelial cells and lymphocytes. Here and there branches of the portal vein are distended with clots, evidently of postmortem origin, consisting of fibrin, polymorphonuclear and endothelial leucocytes. Inspissated bile is present in some of the bile capillaries near the central vein.

A striking feature of this lesion is the presence of masses of streptococci most often within and adjoining the zones of necrotic liver cells. They are found in endothelial cells lining the sinusoids and also in the vessels, extending along them and often filling them.

In this liver we have a lesion uniformly distributed in every lobule, in close relation to the portal areas but occasionally reaching the central vein. This uniformity of distribution would suggest a toxic origin. On the other hand, the numerous clumps of cocci situated in the endothelial cells and in the sinusoids adjoining the affected liver cells strongly favor the view that, in part at least, they bear a causal relationship to the necrotic cells.

The clinical history of this case resembles very closely the case reported by Roger [14] in 1896. In his case, however, the pathological anatomy differed in that the liver was riddled with abscesses.

There is another explanation for this zonal necrosis based on experimental work done by Opie [30] which will be discussed more fully below. He found that by producing a bacteremia in an animal whose liver he had previously injured, he invariably produced a rather characteristic midzonal form of necrosis. Certainly the more common severe lesion caused by the streptococcus toxin is a central necrosis, and of that there is not the slightest evidence in this liver.

CASE 4. (P. M. H. 970, M 1153), a white male, 56 years of age, was operated upon for appendicitis and made an uneventful recovery. Ten months later the gall-bladder containing two concretions was removed. The liver was reported to be small and a piece was excised which histologically showed nothing abnormal. Seven weeks later the patient developed chills and fever which persisted for a month. Jaundice later appeared; and finally ascites developed which required tapping on two occasions. At this time the liver was observed to be definitely enlarged. The patient's condition progressed gradually and eight and a half months after the operation on the gall-bladder he died with an extensive cirrhosis of the liver.

At autopsy the tissues were all deeply jaundiced, the abdomen was distended and the peritoneal cavity contained 6000 cc. of slightly cloudy yellowish fluid containing flakes of fibrin.

The liver, weight 1920 gm., extended 1 cm. below the costal margin. Old adhesions joined the anterior surface of the liver to the under surface of the diaphragm. The left lobe was reduced to a small scarred puckered mass of connective tissue lying to the left of the coronary ligament, which, when sectioned, revealed scar tissue, blood vessels and large bile ducts.

The right lobe was yellowish in color with a fairly nodular surface. It cut with increased resistance, exposing on the fresh surfaces nodules of deep golden yellow which changed to green on exposure to air.

The remaining viscera, with the exception of the spleen which was enlarged and rather lax and weighed 400 gm., showed no noteworthy changes.

Anatomical Diagnoses: Cirrhosis of the liver, peritonitis, ascites and jaundice.

Histological Examination

The liver presents a most unusual appearance. The original lobular architecture is almost entirely replaced by wide interlacing tracts of proliferating bile ducts and connective tissue which isolate small nodules of liver cells composed partly of remnants of former lobules together with regenerated trabeculae showing no orderly structure. These young bile ducts form a most intricate meshwork of channels among themselves, often encircling small groups of liver cells. The bile ducts are definitely abnormal, resembling somewhat the structures seen in primary bile duct tumors. The cells and nuclei are parallel with the lumina, both are distinctly elongated, instead of being rather cuboidal with the nuclei at right angles to the lumina. Occasional clusters of streptococci can be found among the liver cells, some are extracellular, others intracellular, apparently within the cytoplasm of endothelial cells lining the sinusoids. In other fields are small groups of degenerating and necrotic liver cells which are infiltrated with polymorphonuclear and endothelial leucocytes. The interstitial tissue is increased, especially about the new formed bile ducts and also, although to a lesser degree, among the regenerated liver cells. The stroma everywhere is infiltrated with neutrophilic leucocytes, endothelial leucocytes, lymphocytes, occasional eosinophiles and nests of plasma cells.

The striking feature of this case is the extraordinary number of bile ducts present. They are so prominent that they suggest the possibility of a tumor but evidently are not. Small patches of a somewhat similar bile duct formation occur in other forms of cirr-

hosis such as the pigment and syphilitic types, but to nothing like the extent and amount present in this case.

In the relatively common type of toxic cirrhosis following acute yellow atrophy, the bile ducts at the periphery of each lobule grow for a certain distance toward the center and then stop. In the adult they do not produce liver cells and they do not extend indefinitely.

The history of this case strongly suggests infection of the liver. "Seven weeks after cholecystectomy the patient had chills and fever which persisted for a month. After two months he became jaundiced, and one month later developed ascites. He died from cirrhosis of the liver eight and a half months after the operation of cholecystectomy."

Unfortunately the liver was not cultured at the time of the autopsy. The chains of cocci seen in the stained sections may represent simply a terminal bacteremia, or, and what seems to us not improbable, they may have been present in the liver for weeks, possibly having gained entrance to the organ at the time of the cholecystectomy. There seems to be no other way to explain it. It would mean a chronic lesion due to a streptococcus of moderate virulence causing widespread, but not extensive and rapid necrosis.

CASE 5. (B. C. H. 98–211), a young woman who died of pernicious anemia. The immediate clinical history is irrelevant insofar as it has no bearing on an old healed inflammatory process which was found within the liver.

The liver was of normal size and color, but revealed both beneath the capsule and on the cut surface minute grayish areas suggesting small scars.

HISTOLOGICAL EXAMINATION

These small scar-like areas consisted of contracted lobules containing numerous bile ducts but no liver cells. They strongly suggest healed patches of acute yellow atrophy and so far as can be determined from their size, shape, isolation and distribution, are much more likely to have been of infectious than of toxic origin. The lesions at first suggested multiple adenomas of bile duct derivation, but careful study of them later disclosed the contracted lobular arrangement with the portal vessels still evident.

Report of Experimental Work

If we are willing to postulate that streptococci acting locally can produce a definite inflammatory reaction in the liver with degeneration and necrosis of the parenchyma, then one might ask what experimental evidence we have to substantiate such a claim. Furthermore, can we assume in certain cases of streptococcus infection in which one finds inflammatory foci within the liver, but no organisms, that such lesions are actually infectious in origin, only the organisms have been rapidly killed and removed?

We have employed rabbits in our experimental work, but there are certain dangers in attempting to correlate pathological lesions produced in lower animals with those seen in man, in that we have here two biological systems of quite different constitution. The problem becomes still more complicated when we add to these a third living organism — namely an organism so complex and variable as the streptococcus. In attempting, therefore, to answer these two questions, namely, can streptococci produce similar changes in animals, and how long may the organisms survive within these lesions, we report the results of our work with considerable reserve.

Among the earliest investigators in this field of research was Wyssokowitsch [31] who as early as 1886 showed that the endothelial cells of the liver were capable of phagocytosis and would take up bacteria that were injected into the circulating blood.

Many years later this work of Wyssokowitsch's was repeated by Nathan,[32] using not alone bacteria, but collargol and other substances as well. He verified the earlier work on phagocytosis by the Kupffer cells, and demonstrated an active proliferation of these cells followed by a desquamation into the circulating blood.

Roger [14] in 1896, after isolating a streptococcus from abscesses within the liver, made an emulsion with saline and injected this subcutaneously and intravenously into rabbits, but produced no marked demonstrable reaction.

Weaver [33] in 1900 produced a type of cirrhosis in guinea pigs by inoculating a strain of *B. coli* into the portal vein. This type of cirrhosis was characterized by an increase in bile ducts and perilobular connective tissue. His results indicate how critical one must be in interpreting the results obtained in lower animals, because the same organism produced absolutely no lesions in rabbits.

A year later Hektoen [34] reported certain results, confirming the work of Weaver. He produced a similar lesion, using a second organism belonging to the *B. diphtheria* group, and was able to demonstrate the organisms within the early lesions.

As far as we can determine from a review of the literature, Opie [30] was the first to attempt to produce lesions experimentally within the liver by injecting streptococci. When he injected a suspension of streptococci intravenously into dogs, the only appreciable change he found in the liver was a slight deposition of fat within the liver cells. However, if he first inoculated dogs with a small amount of chloroform or phosphorus — an amount which he previously determined to be incapable of producing destructive lesions within the liver — and then followed this a few days later with an intravenous injection of streptococci, he invariably produced extensive midzonal and central necrosis — a type of lesion resembling that of acute yellow atrophy. He explained these lesions on the basis of a combined intoxication, making no attempt to link up the changes with the presence of organisms within the liver.

Recently Moon [28] in an attempt to substantiate his claim that a strain of streptococcus hemolyticus, which he had isolated from the liver of a young child with cirrhosis was the causative agent in this disease, injected a suspension subcutaneously and intraperitoneally into rabbits and produced degenerative lesions in the liver in which he demonstrated the organisms.

Regarding the second question relative to the period of survival of organisms within inflammatory lesions in the liver, some information is to be found in a report by Schwarz.[35] This worker injected into mice an organism of the diphtheroid group which he had isolated from a child's liver. He killed these mice at intervals of one to seven days following the injection. After twenty-four hours the liver was riddled with minute inflammatory foci teeming with organisms; as the interval of time increased, the number of organisms diminished, and after seven days he was unable to demonstrate organisms within the lesion.

Kyes [36] studied the fate of pneumococci after intravenous inoculation into the pigeon, which is naturally resistant to this organism. He made careful studies of various organs and found that the organisms were quickly removed from the circulating blood and localized within the endothelial cells of both spleen and liver. In addition he

showed that at the end of one hundred and twelve hours the cocci were completely destroyed.

We began our experimental work using a group of guinea pigs, but because the livers of these animals were practically refractory to infection, it was necessary to select rabbits, which proved to be more satisfactory.

A pure culture of streptococcus hemolyticus which had been isolated from the throat of a patient with scarlet fever was used throughout the experiments. On blood agar the colonies were quite typical, being small, gray and opaque and surrounded by a wide clear ring of hemolysis.

A saline suspension was made from a growth on blood agar slants as we wished to inject the organism as free from toxin as possible. The quantity injected varied from 3 to 4 cc. of a moderately heavy uniform suspension.

As a control, an equal quantity of a similar suspension that had been heated to 60° C for one hour, and proved sterile, was introduced into the rabbit's liver under precisely the same conditions. These animals lived and showed neither gross nor histological lesions within the liver.

The operating technique was simplified as much as possible. The abdomen was shaved and using asceptic precautions a small opening was made into the peritoneal cavity. A loop of the small intestine was drawn through the opening, thereby exposing branches of the mesenteric artery and portal vein. The vein was freed for about 1 cm. from the surrounding fat and connective tissue and ligated at the distal end of this exposed section. A second ligature was loosely tied about the vein proximal to the first. The next step was to inject the organisms into the vein, and for this a small Luer syringe with a No. 24 gauge needle proved most suitable. Just before withdrawing the needle the proximal ligature was tightly tied. The intestines were replaced and the abdominal wall closed with a double row of continuous sutures.

The first rabbit died after eighteen hours, the second after twenty. The third, which made a good recovery and appeared quite healthy, was killed at the end of forty-eight hours. The fourth rabbit also made a good recovery but was killed after five days.

Blood cultures taken from the ear veins of these animals at the end of twelve hours showed streptococci in pure culture. Further cultures taken after forty-eight and seventy-two hours were negative.

The autopsy blood cultures from the first and second rabbits, which had died at the end of eighteen and twenty hours respectively, were sterile. Cultures taken directly from the liver in both cases yielded a few typical colonies on a blood agar plate. Smears made from scrapings of the freshly cut surfaces of both livers, showed in addition to liver cells, chains of cocci and many polymorphonuclear leucocytes. A blood culture taken from the third rabbit at the time of the autopsy forty-eight hours after the injection was sterile, while only three colonies were grown on a blood agar plate after being heavily streaked with a swab that had been inserted deeply into the liver parenchyma. A smear made directly from the liver at this time showed liver cells, cellular débris, polymorphonuclear and endothelial leucocytes, and a few poorly stained and questionable clusters of organisms suggesting streptococci.

The fourth rabbit, from which sterile blood cultures had been obtained at forty-eight and seventy-two hours after the injection, was autopsied at the end of five days. Cultures taken from the heart, and liver, as well as smears from the latter organ revealed no streptococci.

In summing up our bacteriological results we find that at twenty-four hours living organisms had to a great extent disappeared from the circulating blood and the liver; at forty-eight hours the number of viable streptococci in the liver was practically negligible, and lastly at the end of five days all cultures from different sources, as well as smears taken directly from the liver showed no trace of streptococci.

The rapidity with which streptococci have been destroyed in the liver may largely explain some of the histological characteristics of the lesions, and particularly the fact which has been previously stressed in this paper that it has often been quite impossible to demonstrate organisms histologically in the lesions.

Gross Examination: Within the first twenty-four hours there was little to suggest any severe injury to the liver. The organ was normal in size, the capsule smooth and the cut surface uniformly congested and rather soft. In the forty-eight hour animal, small areas beneath the capsule showed up as a yellowish stippling or a very fine network of delicate lines that were slightly raised above the surrounding liver tissue. The cut surface varied considerably in different lobes; some areas showed simply congestion, edema, and a loss of the finer mark-

ings, other areas were traversed by thin yellow lines, and still others were mottled with small yellowish foci which varied in size and contour. After five days, the liver was normal in size, moderately firm and dark reddish brown. The surface was smooth, except for three yellowish depressed areas, each about 2 to 3 mm. in diameter.

Microscopic Examination: In Rabbit 1, dead at the end of eighteen hours, one finds chains of cocci up to a dozen or more in many of the endothelial cells lining the sinusoids. The reaction to these consists in an accumulation of polymorphonuclear and endothelial leucocytes, together with small clumps of fibrin within the vessels. Where leucocytes have clustered in adjoining sinusoids, the isolated liver cells often show necrobiotic changes and necrosis. Such lesions are found in any part of the lobule, even adjoining the hepatic vein, but they occur most abundantly at the periphery of the lobules close to the portal vessels. These peripheral lesions may suggest in their extent and distribution, small zones of infarction, but the inflammatory reaction which is uniformly distributed throughout this damaged area differentiates them clearly from bland areas of infarction.

In Rabbit 2, dead at the end of twenty hours, streptococci are more difficult to find. The lesions are more numerous and a little larger. Many of the necrotic liver cells have already disappeared, and their places are occupied by minute islet-like collections of endothelial leucocytes.

In Rabbit 3, killed forty-eight hours after the injection, numerous large and small lesions are present. Some nearly equal the size of a lobule. These large lesions are composed of necrotic liver cells among which polymorphonuclear and endothelial leucocytes are invading and digesting the cellular débris. At the periphery of these lesions the necrotic liver cells have largely disappeared, and here accumulations of endothelial leucocytes are more prominent than centrally where the polymorphonuclear leucocytes are in greater evidence. The smaller lesions represent a later stage in this reparative process, and are merely nests of endothelial leucocytes which have removed the dead liver cells. A very few streptococci can still be found in a few of the lesions.

In Rabbit 4, killed after five days, only small lesions are present. They consist of accumulations of endothelial leucocytes and signify a late stage of repair. Either the lesions were originally very small,

or neighboring liver cells have regenerated and replaced those that were destroyed.

In summarizing these histological lesions we find that they are essentially destructive and focal in character, and in none of the livers was there a suggestion of a lesion uniformly limited to the central zones of all lobules such as is seen in toxic hepatitis resulting from chemical intoxication or severe bacterial toxemias. In other words we are dealing with a pathological condition of the liver in which the injury is the result of the immediate presence of the organisms within the lesions themselves.

Pathological Physiology

Before entering into a general discussion of inflammatory lesions within the liver, it seems not at all irrelevant at this point to say a word about the pathological physiology of the liver in cases of streptococcus infection. Since this organ constitutes the largest gland of internal metabolism within the body and is directly or indirectly involved in the metabolism of proteins, fats and carbohydrates, any alteration in function of the liver cell, with or without histological signs, might be considered as sufficient to interfere with the metabolism of any one or all of these substances. We shall not go into this phase of the problem fully, but merely mention a few of the important functional changes which at times are manifested as clinical signs and symptoms.

Hildebrandt [37] in 1910, made the observation that many cases of scarlet fever showed an appreciable increase in the urobilin content of the urine. Such patients may show no trace of jaundice and no demonstrable bilirubinuria. He considered two possibilities in explaining this urobilinuria: first and more important as the result of a functional insufficiency on the part of the liver cell, and secondly, though probably merely as a contributory factor, by the increased destruction of red blood cells. He reported the findings in one liver from one case which terminated fatally. This organ was large, swollen and edematous, and microscopically revealed scattered patches of necrosis. He described these changes as a form of "parenchymatous hepatitis," and quoted Litter who believed that in instances where destruction was more widespread the liver would simulate the picture of acute yellow atrophy and the patient would

show corresponding clinical signs and symptoms, with jaundice and increased bilirubin in the circulating blood.

Schelenz [38] several years later followed up this work of Hildebrandt, and reported that the liver would appear to be more severely affected in some epidemics of scarlet fever than in others. This simulates an observation which has been made repeatedly in regard to inflammatory lesions of the kidney complicating scarlet fever. This investigator reported a fatal case of scarlet fever in a young child who showed a very high urobilin excretion. The liver parenchyma revealed a slight degenerative change, and a diffuse interstitial hepatitis.

In cases of streptococcus infection there are usually no constant clinical signs and symptoms referable to functional or morphological changes within the liver. That is, the liver is involved to such a slight degree as to be clinically unrecognizable.

Where the liver is damaged it is probable that the secretion of urobilin is not the only functional alteration of secretion that occurs in the more severe infections. Smyth and Whipple [39] have demonstrated the marked influence that mild chloroform poisoning has on bile salt secretion. Dogs, which had received small doses of chloroform, did not show the slightest clinical indisposition, and yet the bile salt secretion was greatly reduced. Microscopic examination of the livers at this time showed only very slight degenerative changes within the liver cells in the central zones of the lobules.

Whipple and Smith [40] have indicated that an important function of the liver cell is to group together the animo acids to join the precursors of hemoglobin which in turn are utilized by the marrow cells in turning out the finished red blood cells into the circulation. This function of the liver cell, like that of bile salt secretion and the secretion of urobilin and bilirubin, is diminished in liver cells showing slight degenerative changes and would therefore probably be altered in streptococcus hepatitis.

Discussion

One of the most interesting characteristics of the liver is the resistance it shows to infection. Indeed how often at autopsy one sees acute suppurative inflammatory lesions in different parts of the body, severe septicemias and septicopyemias, diffuse inflammatory

reactions within the gastro-intestinal tract, sloughing tumors and ragged ulcers — and yet the liver apparently unharmed. Certainly we may say that the manner in which the liver handles massive infection is scarcely to be seen in any other organ in the body. This very fact, namely the rarity of inflammatory lesions within the liver, coupled with the rather unusual character of these lesions when they do occur, makes the study of this organ one of the most interesting problems in general pathology.

What structures are to be found in the liver which are not common to most organs which may play an important rôle in preventing inflammations from gaining a foothold? Certainly the most important factor is the presence of a very highly developed and healthy system of endothelial cells. But it is not alone the mesenchymal portion of the liver that is bound up with this protective mechanism, it is definitely supported by the integrity of the liver cells and a very rich blood supply. But after all, this protection has its limits: we see this in the occasional colon infection extending out from the terminal bile ducts, in the metastatic abscesses following suppurative phlebitis of the portal vein, in the amebic and actinomyces infections, and also in tuberculosis, syphilis, typhoid and others, and lastly, as we have attempted to point out in this paper, we see this occasionally in streptococcus infection.

We have presented the lesions found in five different livers. Two of the three acute cases showed a rather acute inflammatory reaction with degeneration, necrosis of liver cells and an active cellular infiltration in which streptococci were demonstrable within the lesions.

The remaining two livers contain very unusual lesions which may be considered distinctly puzzling. One of these is probably a variety of a chronic lesion due to the immediate presence of streptococci within the liver, whereas the other may perhaps be considered a healed type of lesion due to a similar organism.

These five cases, two of them certainly and perhaps all, due to the immediate presence and action of streptococci, are presented for the purpose of calling attention to these pathological processes which might be overlooked or misinterpreted.

In our short series of experiments we have attempted — with certain reservations — to correlate lesions which may be produced in animals with lesions found in man. Lastly, in regard to the survival period of streptococci within the animal liver, considerable

light is thrown on the interpretation of the rarity with which one can demonstrate organisms within the lesions in man.

It should be pointed out clearly that absolutely no attempt has been made to explain cirrhosis of the liver in its broad sense, as a chronic or healed inflammatory lesion of infectious origin. On the contrary, the points that are particularly emphasized are first that an acute inflammation can occur in the liver as a result of the actual presence of streptococci within this organ; and second, that with extensive destruction of liver cells, followed by a reparative proliferation of connective tissue and bile ducts, wide tracts of sclerosis can be produced, giving a picture which resembles in many respects the healed stages of acute yellow atrophy.

SUMMARY

1. The more common inflammatory changes in the liver in cases of streptococcus infection with and without a septicemia are described.

2. Emphasis is laid on a less common lesion of which three cases are given in detail. This is characterized by focal or diffuse areas of liver tissue showing necrobiotic changes and necrosis, infiltrated with an inflammatory exudate. A Gram-Weigert stain shows streptococci in large numbers in the lesions of two of these livers.

3. The similarity of this lesion to the histological picture at times encountered in acute yellow atrophy is discussed, and the suggestion is made that a careful bacteriological search of the liver in the fixed preparation together with a culture of the liver at the time of the autopsy might reveal bacteria within the lesions more commonly than is suspected — particularly in those cases of so-called acute yellow atrophy showing a very irregular distribution of the lesion — a condition that is extremely difficult to explain purely on the basis of a circulating toxin in the blood.

4. Another case is described with a chronic inflammatory reaction within the liver, showing on the one hand degeneration, necrosis, exudation and bacteria, and on the other a very active proliferation of bile ducts and connective tissue. This case is presented more for discussion than as a proved case of chronic progressive cirrhosis of infectious origin.

5. The last point that is considered is the histological and gross changes which one may find in the healed stage of these acute and chronic inflammatory lesions.

6. The second part of the paper is devoted to the results of experimental work. A streptococcus obtained from an early case of scarlet fever, was injected free of toxin into one of the radicles of the portal veins of both guinea pigs and rabbits. The animals were killed at varying intervals, and the lesions produced, together with the results of bacteriological studies, are fully described and compared with the lesions seen in human cases.

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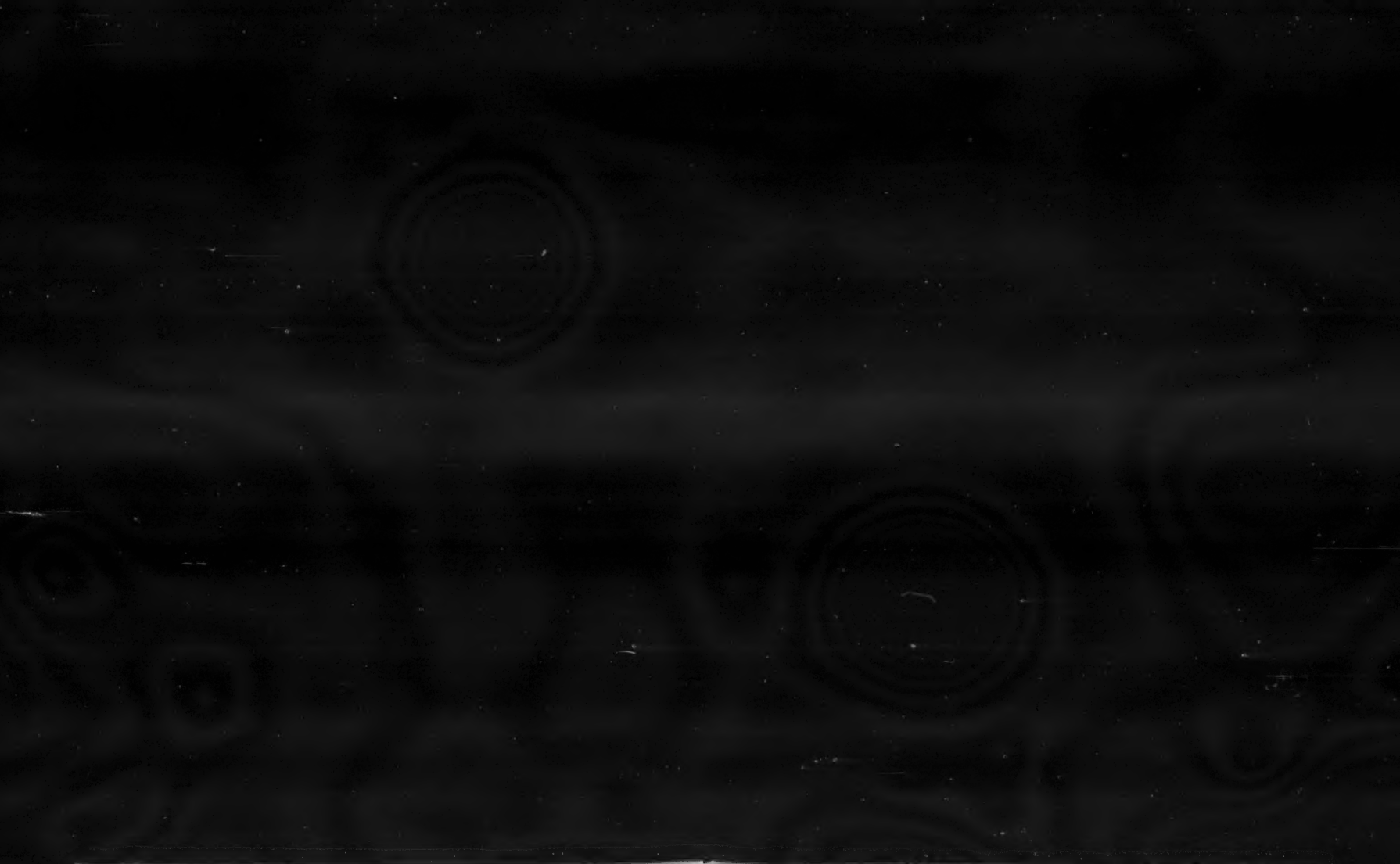
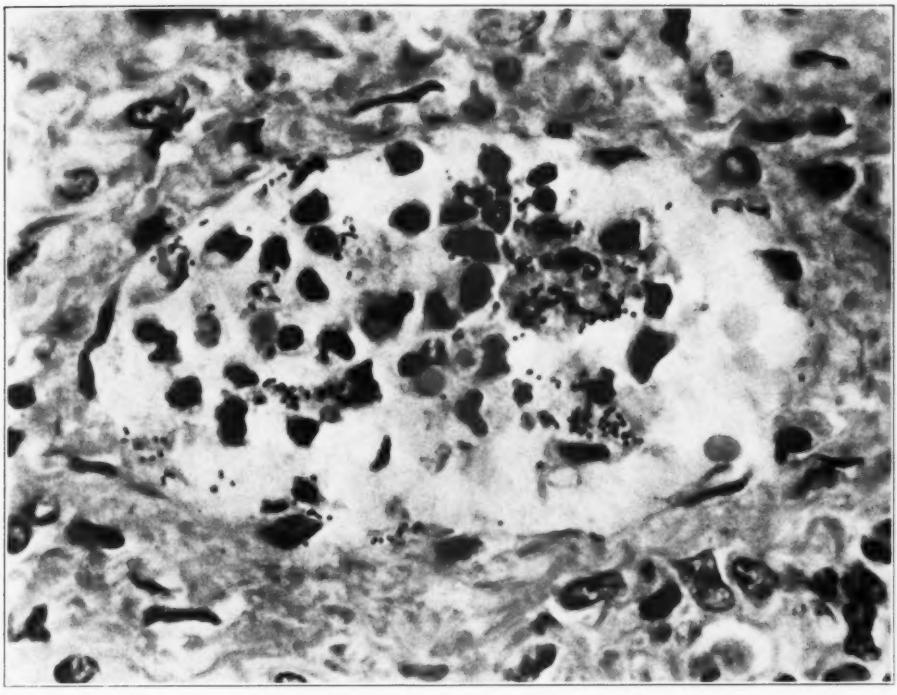
DESCRIPTION OF PLATES

PLATE 55

FIG. 1. Case 1. Masses of streptococci, largely in endothelial leucocytes, within a portal vein. × 1000.

FIG. 2. Case 1. The sinusoids of the liver contain numerous streptococci of which many are included in the lining endothelial cells and in endothelial leucocytes filling the vessels. × 1000.





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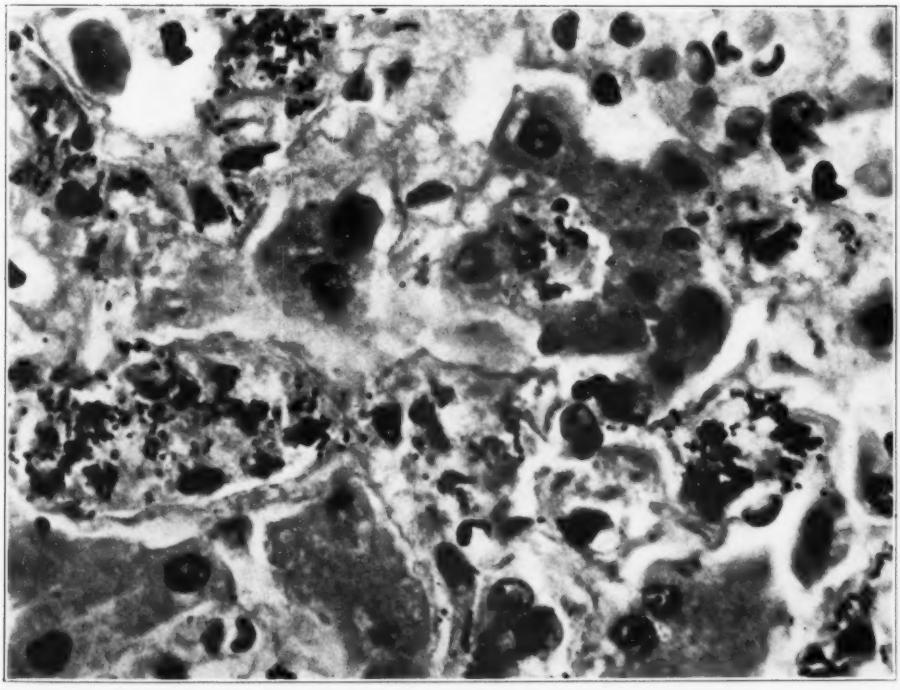


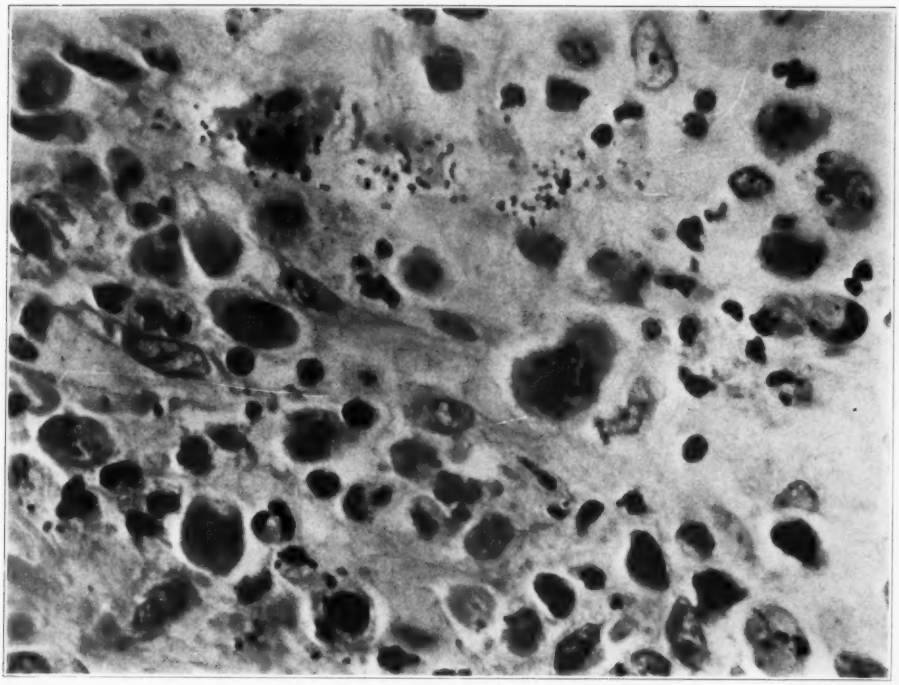
2

MacMahon and Mallory Streptococcus Hepatitis

PLATE 56

FIG. 3. Case 1. An area in a lobule where the necrotic liver cells have to a large extent disappeared. Streptococci are still persistent in moderate numbers, largely in endothelial leucocytes. × 1000.

FIG. 4. Case 2. The edge of one of the two areas of necrosis involving many lobules. All of the liver cells have been killed and are being removed by the action of leucocytes. Only the bile ducts and stroma persist. The adjoining liver tissue is uninjured. × 40.



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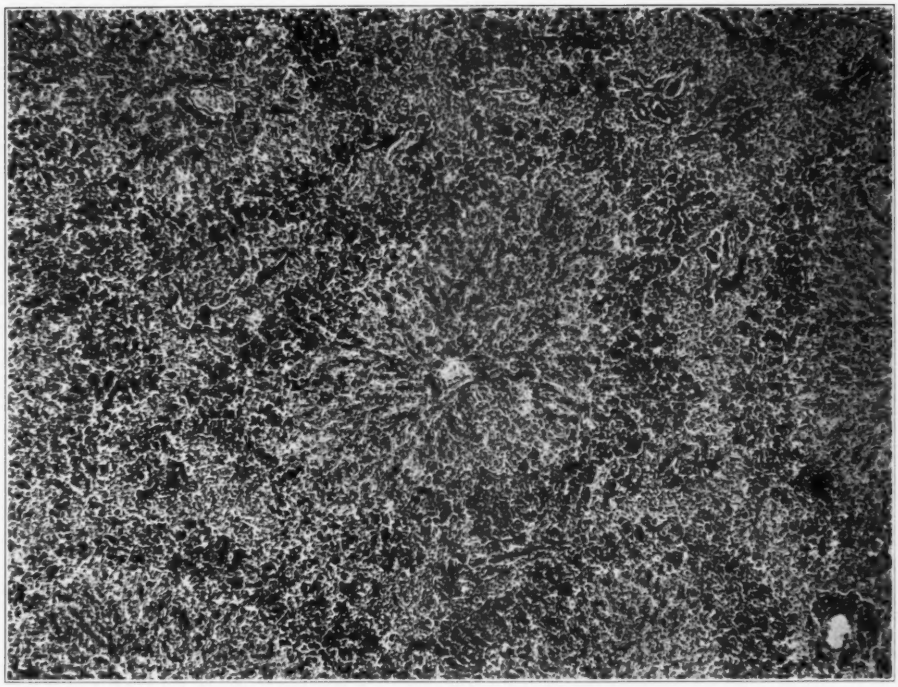
4

MacMahon and Mallory Streptococcus Hepatitis

PLATE 57

FIG. 5. Case 3. The liver cells are necrotic in the peripheries of the lobules, presenting in places a zonal arrangement. × 60.

FIG. 6. Case 3. A high power view of a small area in the necrotic zone. The nuclei of the liver cells have mostly disappeared. The sinusoids contain large clumps of streptococci. × 1000.



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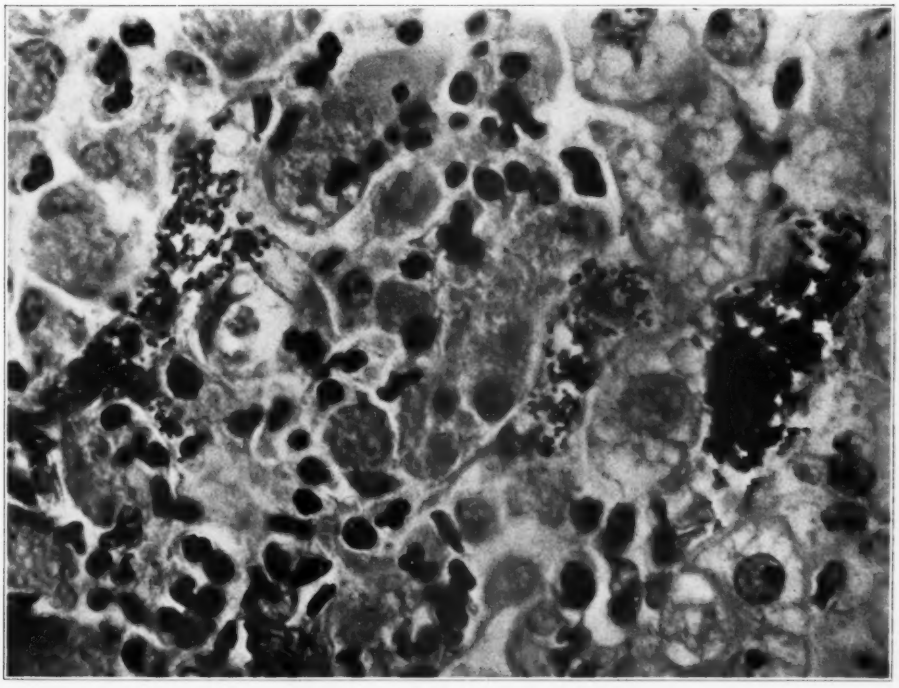


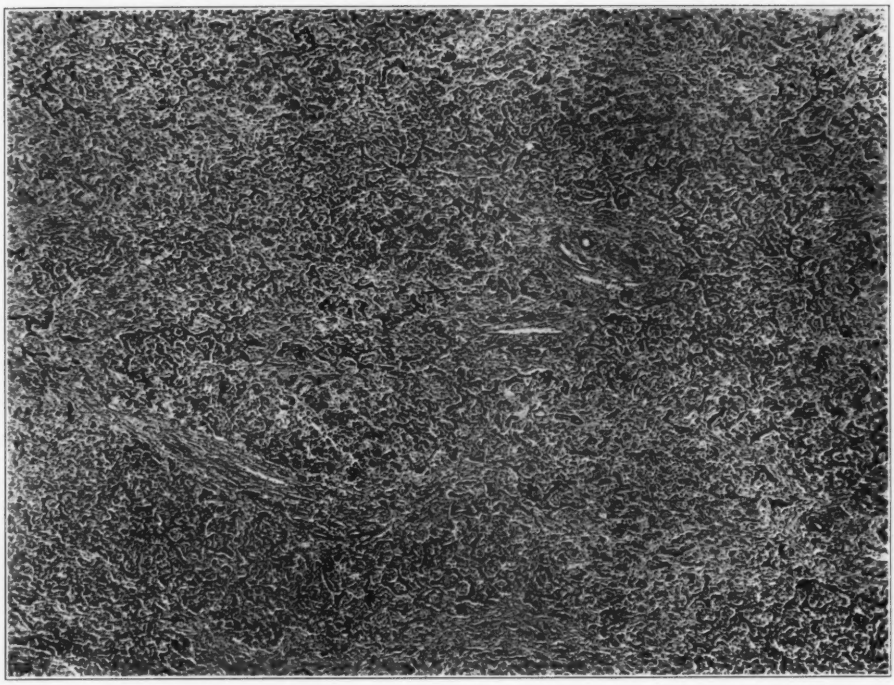
6

MacMahon and Mallory Streptococcus Hepatitis

Plate 58

Fig. 7. Case 4. A low power view showing the extensive formation of bile ducts. An occasional portal area can be made out. × 50.

Fig. 8. Case 4. Marked formation of bile ducts. Only small islands of liver cells are present. × 60.



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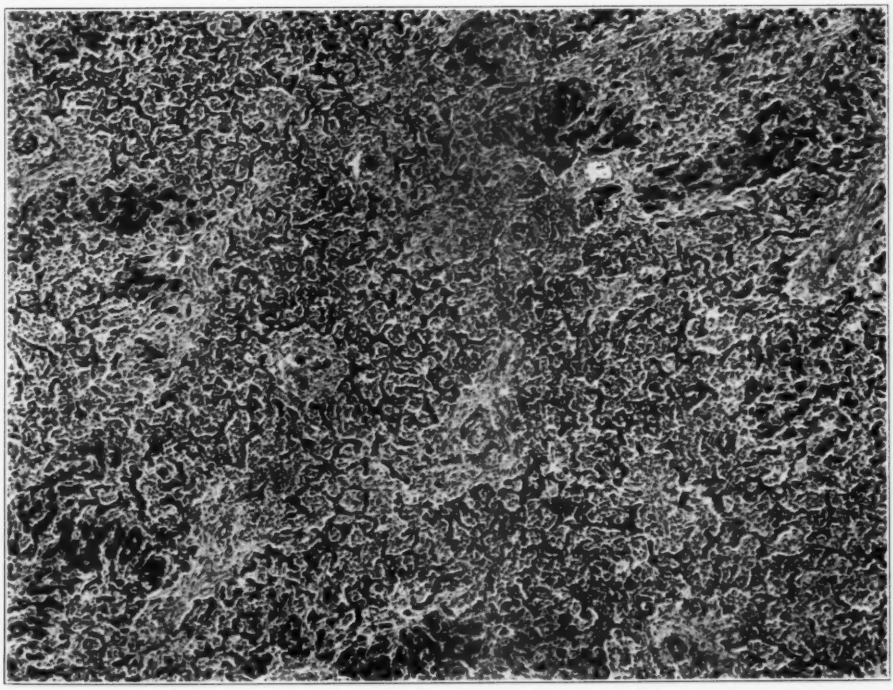


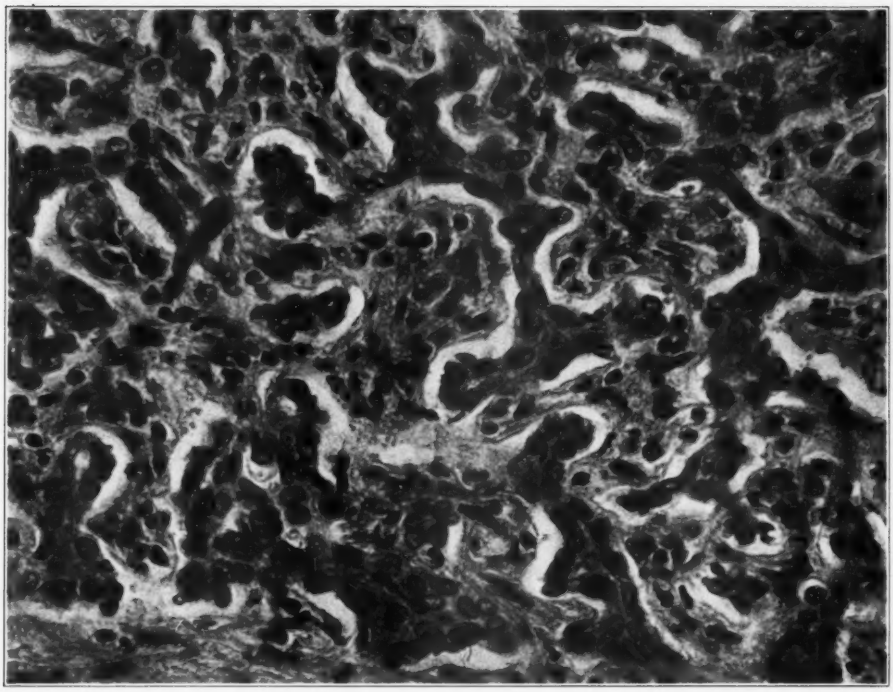
8

MacMahon and Mallory Streptococcus Hepatitis

PLATE 59

FIG. 9. Case 4. High power view of network of bile ducts. The stroma is fairly abundant. × 500.

FIG. 10. Case 4. Masses of streptococci mostly contained within endothelial cells lining the sinusoids. × 1000.



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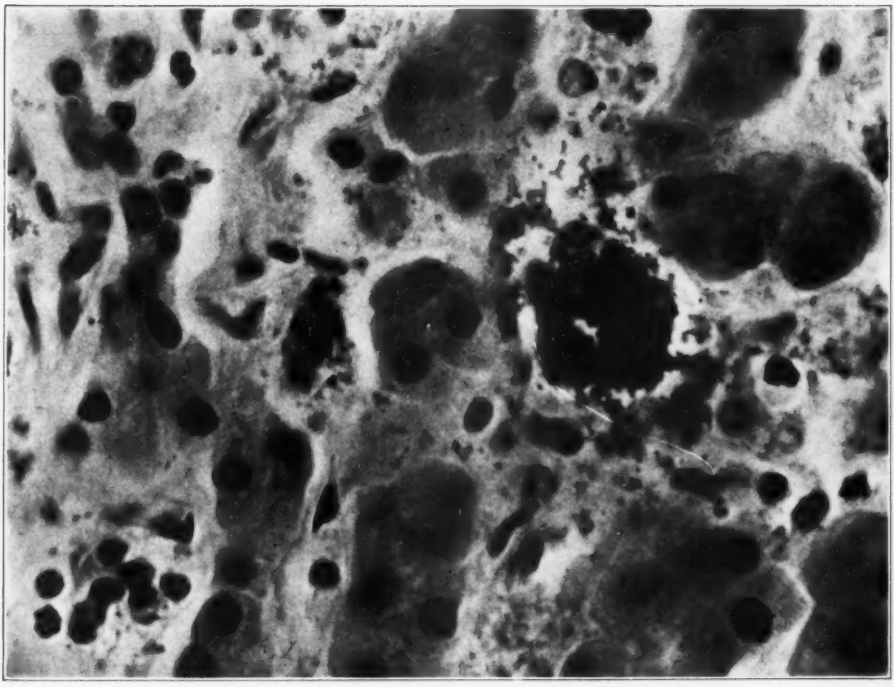

10

MacMahon and Mallory Streptococcus Hepatitis